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A RATIONAL APPROACH TO THE TREATMENT OF RHEUMATOID ARTHRITIS: INTRODUCTION

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RHEUMATOID ARTHRITIS is a highly complex systemic disorder of unknown etiology. It is characterized by great variations in disease activity and therapeutic response which make it difficult to evaluate the results of treatment. As yet no treatment has proved to be consistently effective. The favorable results that have been achieved with various therapeutic agents often are only temporary and, when relapse occurs, unfortunately an increased dosage of the therapeutic agent does little more than produce toxic reactions.

We have investigated during the past six years the effects of drugs on rheumatoid arthritis of varying severity. The effects of intravenous *nitrogen mustard** have been studied for six years (part I), intraarticular *nitrogen mustard** for two years (part II), the hydrazides *isoniazid* and *iproniazid*** for five years (part III), and the antimalarial agents *hydroxychloroquine sulfate*† and *chloroquine phosphate*†† for two years (part IV). The drugs were administered singly and

Mustargen hydrochloride, Merck Sharp & Dohme, Division of Merck & Co., Inc.
**Marsilid phosphate, Hoffmann-La Roche, Inc.*
†Plaquenil sulfate, Winthrop Laboratories.
††Aralen phosphate, Winthrop Laboratories.

also in combination with *corticotropin* (*ACTH*) and various corticosteroids[a-g]—*cortisone acetate*,[a] *hydrocortisone*,[b] *prednisone*,[c] *prednisolone*,[d] *hydrocortisone acetate*,[e] *hydrocortisone tertiary-butylacetate*,[f] and *prednisolone tertiary-butylacetate*.[g] In combination, each drug usually was administered in a dose that alone had little suppressing effect on disease activity. The effects of each drug were observed for one year or longer, during which time the desirable and undesirable actions were evaluated. Combinations of drugs, dosages, and routes of administration were determined which would most effectively suppress disease activity and cause the least number of toxic reactions. Corticotropin and corticosteroid were used sparingly and temporarily in an attempt to avoid undesirable side effects. The combinations of drugs were altered in accordance with the individually fluctuating state of the disease in each patient. The entire program of chemotherapy as now conducted for patients with active rheumatoid arthritis of varying severity is discussed in part V.

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[a]*Cortone acetate, Merck Sharp & Dohme, Division of Merck & Co., Inc.*

[b]*Hydrocortone, Merck Sharp & Dohme, Division of Merck & Co., Inc.*

[c]*Meticorten, Schering Corporation.*

[d]*Meticortelone, Schering Corporation; Stearane, Pfizer Laboratories, Division of Chas. Pfizer & Co., Inc.*

[e]*Hydrocortone acetate, Merck Sharp & Dohme, Division of Merck & Co., Inc.*

[f]*Hydrocortone-T.B.A., Merck Sharp & Dohme, Division of Merck & Co., Inc.*

[g]*Hydeltra-T.B.A., Merck Sharp & Dohme, Division of Merck & Co., Inc.*

I. INTRAVENOUS ADMINISTRATION OF NITROGEN MUSTARD ALONE AND WITH CORTICOTROPIN FOR RHEUMATOID ARTHRITIS

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NITROGEN MUSTARD has been used for a variety of clinical diseases that manifest tissue and vascular reactivity, such as rheumatoid arthritis, rheumatic fever, systemic lupus erythematosus, periarteritis nodosa, dermatomyositis, and acute and subacute glomerulonephritis.[1-9] The action of nitrogen mustard (hereinafter termed *HN_2*) is inhibitory on accelerated growth of normal as well as of neoplastic cells.[10] Chemically, HN_2 is methyl-bis-(β-chloroethyl)-amine hydrochloride, an alkylating agent that replaces hydrogen with alkyl groups in organic molecules; it contains two reactive ethyleneimine groups[10] that inhibit actively growing and proliferating cells.

The basic mechanism of the inhibition is not understood; however, it has been postulated[11] that inhibition of enzymatic activity might account for its action, although to inhibit most enzymatic systems in vitro, a far higher concentration of HN_2 is needed than is possible to achieve in vivo. A more likely theory[12] takes cognizance of the high degree of reactivity of HN_2 with specific nucleoproteins that are essential to cellular reproduction. Viruses that are rich in nucleoproteins are highly susceptible to irreversible inactivation by HN_2, a susceptibility that appears to be directly related to viral nucleic acids. Viruses that contain largely or exclusively desoxyribonucleic acid are more readily inactivated by HN_2 than are those that contain predominantly ribonucleic acid. This selectivity of action suggests that HN_2 may act directly on desoxyribonucleic acid and, by interfering with the anabolism of this important nuclear constituent, render the cells nonproliferative.[11]

After intravenous administration of HN_2, development of the Shwartzman phenomenon is suppressed.[13,14] Becker[15] postulated that the mechanism of suppression is exerted through the reticuloendothelial system, primarily the vascular endothelium: these endothelial cells being rendered anergic are unable to react in a way that would be self-destructive.

Clinically, when the usual total dose of 0.4 mg. HN_2 per kilogram of body weight is administered intravenously over a period of four days, the only normal tissues that may be significantly suppressed are lymphoid tissue and bone marrow. McCarthy[16] was of the opinion that the combined use of corticotropin (hereinafter termed *ACTH*) and HN_2 reduced the suppressive effect of HN_2 on bone marrow, and alleviated nausea and vomiting. His patients with malignant lesions were given three or more total doses of 0.5 mg. HN_2 per kilogram of body weight within one year. Rollins and Shaw[17] did not confirm McCarthy's observation, but in their patients lymphopenia and leukopenia were transient and were not considered clinically significant.

We investigated the effects on rheumatoid arthritis of intravenously administered HN_2 during 1950 and 1951, and the combined administration of HN_2 with ACTH during 1951 through 1955.

Nitrogen Mustard

Material and methods. The series comprised 17 patients who had active rheumatoid arthritis for from 1 to 13 years. Four patients had grade 1 disease, four had grade 2, six had grade 3, and three had grade 4 disease.* In all patients there was involvement of at least two or more joints, manifested by persistent joint swelling and pain on motion. Activity was restricted severely in 4, moderately in 10, and slightly in 3 patients.

All patients were hospitalized throughout the course of treatment. HN_2, 1 mg. per milliliter in normal saline solution, was administered intravenously. Amobarbital sodium**, 0.20 gm., was given intramuscularly at the same time to alleviate nausea and vomiting. Ten patients received 0.1 mg. per kilogram of body weight on alternate days, and seven patients received 0.05 mg. per kilogram of body weight daily, for a total dosage of 0.4 mg. per kilogram of body weight. Each patient received a total of from 15 to 25 mg. HN_2.

Laboratory and clinical findings. During treatment it was noted that white blood cell counts that had been elevated usually dropped to normal; normal total white blood cell counts usually did not change significantly. The differential blood count in most instances revealed a slight-to-moderate decrease in the percentage of circulating lymphocytes. Frequently the hemoglobin content increased within from 3 to 10 days after the administration of HN_2. The apparent rise in hemoglobin content was accompanied by a rapid decrease in the serum polysaccharide-protein ratio[19-21] and a fall in the erythrocyte sedimentation rate (Rourke-Ernstene method[22]). There were also a drop in serum alpha-2 globulin and a rapid reciprocal rise in albumin determined by electrophoresis.[23] Mild weakness usually occurred four to seven days after the administration of HN_2 and disappeared two to four weeks later.

One and three months after the termination of intravenous therapy, studies were made of 5 of the 17 patients for evidence of stimulation of adrenocortical function. No significant changes were demonstrated in the urinary excretion of 17-ketosteroids, in the uric acid-creatinine ratio, or in the percentage decrease of circulating eosinophils.

In all patients, redness, warmth, swelling, and tenderness of the joints disappeared within two to seven days after the onset of treatment. Temperatures that had been elevated dropped to normal within 24 to 48 hours. Aching and stiffness disappeared completely in eight patients, were moderately relieved in five, and persisted in four patients. Within six months after the administration

Grades of disease [18] are described in the footnote of Table 1.

***Amytal sodium, Eli Lilly & Co.*

Table 1.—*Data for 17 patients given HN_2 intravenously for rheumatoid arthritis*

Number of patients	Grade*	Class**				Response† to treatment after: 2 weeks				2 months				4 months				6 months			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
		Number of patients																			
4	1	0	2	2	0	3	1	0	0	2	2	0	0	2	1	1	0	1	2	1	0
4	2	0	1	3	0	3	1	0	0	3	1	0	0	1	1	2	0	1	1	2	0
6	3	0	0	3	3	2	2	2	0	0	4	2	0	0	3	2	1	0	0	4	2
3	4	0	0	2	1	0	1	2	0	0	0	2	1	0	0	2	1	0	0	2	1

Adapted in part from A.R.A. classification.[18]

**Grade:* *1—joint swelling, no joint destruction; 2—minimal cartilage or bone destruction; 3—subluxation; 4—ankylosis.*

***Class:* *1—asymptomatic, full activity; 2—minor symptoms, full activity; 3—moderate symptoms, light activity; 4—moderate-to-severe symptoms, light-to-no activity.*

†*Response:* *1—(excellent) asymptomatic; 2—(good) minor aches and pains; 3—(fair) slight persistence of joint tenderness and swelling; 4—(poor) moderate persistence or no relief of joint pain and swelling.*

of HN_2, 15 of the 17 patients had recurrence of symptoms in varying degrees of severity. Only two patients have remained asymptomatic for more than five years. Data for the 17 patients are summarized in Table 1.

Contraindications. Contraindications to the use of this amount of HN_2 in rheumatoid arthritis are infrequent. It is not recommended in advanced disease where there is little or no inflammation. If superficial veins are small or permeable, the drug is not administered. If an associated blood dyscrasia is present, HN_2 should be used with caution because of increased sensitivity of the hematopoietic system.

Comment. HN_2 is a powerful anti-inflammatory agent when administered intravenously to patients with acute or subacute rheumatoid arthritis. Because the disease activity is only temporarily suppressed, the value of the drug is limited.

Nitrogen Mustard Combined with Corticotropin

ACTH has been used successfully to suppress the inflammatory activity of rheumatoid arthritis. The metabolic effects that occur immediately after administration of ACTH result from the release of adrenocortical steroids and, in general, are similar to those that occur after administration of cortisone. Although the exact nature of the secretion of the adrenal cortex is unknown, on the basis of current evidence suppression of inflammation is believed to result from the release of hydrocortisone by ACTH. Aqueous preparations are rapidly absorbed and metabolized, necessitating multiple daily injections, but mixtures with gelatins and zinc are more slowly absorbed and consequently require fewer injections. Aqueous ACTH, 20 to 25 units diluted in 5 per cent dextrose solution, administered intravenously may cause a dramatically rapid suppression of symptoms related to disease activity, but this procedure has no apparent place in the continuing treatment of rheumatoid arthritis.[24] The dosage of intravenously administered ACTH that maximally stimulates the adrenal gland is considered to be 20 to 25 units administered continuously over a period of eight hours.[25] This amount of ACTH given intravenously daily for one week or more is likely to result in a state of acute hypercorticalism.

Ten patients were given 20 units and 10 patients were given 10 units of aqueous ACTH intravenously in 1 liter of 5 per cent dextrose in water daily during a six-hour period for 10 days. Seven of the 10 patients receiving 20 units showed early signs of acute hypercorticalism between the sixth and eighth days of treatment, and 1 of the 10 patients receiving 10 units of ACTH showed similar characteristics after the tenth day. Joint manifestations and general symptoms subsided rapidly in all patients receiving 20 units and in six patients receiving 10 units of ACTH. Relapse was rapid in all instances, usually occurring within from one to five days after ACTH had been discontinued.

Inasmuch as HN_2 or ACTH when administered intravenously causes rapid suppression of inflammation in rheumatoid arthritis, we decided to observe the effect of these agents administered simultaneously, but each in smaller doses

than those used when it was administered alone, in order to reduce the possibility of toxic reactions or side effects from either drug.

Material and methods. Two hundred sixty-three patients who have received combined ACTH and HN_2 infusions since June 1951 were observed for four or more years. In this group were 221 patients who had various stages of rheumatoid arthritis, 18 patients who had both rheumatoid arthritis and a positive test for lupus erythematosus, 12 patients who had psoriasis and rheumatoid arthritis, 8 patients who had palindromic rheumatism, and 4 patients who were more than 16 years of age and who had active Still's disease. Table 2 summarizes the data of the study.

The total dosage of HN_2 for a course (five to seven days) was 0.2 mg. per kilogram, or 2 to 3 mg. daily. The usual dosage of ACTH was 10 units diluted in 500 ml. 5 per cent dextrose in water and administered intravenously over a period of four hours. One-half hour after the intravenous administration of ACTH had been started, HN_2 was given intravenously directly through the rubber tubing used for the ACTH. To alleviate nausea and vomiting, 50 mg. of promazine hydrochloride* was given orally one hour before intravenous treatment was begun.

Results. The effects of these drugs were evaluated two weeks after injection (Table 2), inasmuch as the action desired was quick suppression of systemic symptoms and joint manifestations. In 88 per cent of 263 patients there was rapid and complete or almost complete relief of joint manifestations, toxicity, and fever. Disease activity, as reflected by an increase in the erythrocyte sedimentation rate, serum alpha-2 globulin, and serum polysaccharide-protein ratio, lessened but did not subside completely. Frequently in acute or subacute rheumatoid arthritis, lupus erythematosus, and occasionally in palindromic rheumatism, the response to these therapeutic agents was dramatic and appeared within from 24 to 48 hours. The most difficult form of arthritis to suppress was rheumatoid arthritis associated with psoriasis. In approximately 40 per cent of the 221 patients with rheumatoid arthritis the disease became temporarily migratory during induction therapy. Often these migratory joint manifestations appeared after having been absent for a number of months or years. Fleeting, erythematous, maculopapular dermatoses appeared in approximately 20 per cent of these 221 patients. The lesions were most prominent over the face, chest, arms, and legs. The temperature was elevated above 100 degrees F. in 71 per cent of the 263 patients and fell rapidly to normal in 88 per cent of this group within seven days after therapy was begun. In the majority of cases other medication, to be described, maintained the suppressed state satisfactorily; but in 11 per cent or 28 of the 263 patients a second course of combined ACTH and HN_2 was given within one year.

Toxic reactions were limited to nausea (occurring in approximately 40 per cent of the patients), vomiting (occurring in approximately 10 per cent), and generalized urticaria, believed to be due to ACTH (occurring in less than 2 per cent).

Sparine hydrochloride, Wyeth Laboratories.

Table 2.—*Data for 263 patients given ACTH and HN_2 intravenously for rheumatoid arthritis*

Number of patients	Diagnosis	Grade*				Class**				Response† after 2 weeks of therapy			
		1	2	3	4	1	2	3	4	1	2	3	4
221	Rheumatoid arthritis	37	60	83	41	0	71	102	48	161	43	11	6
18	Rheumatoid arthritis with lupus erythematosus	6	12	0	0	0	13	5	0	15	2	1	0
12	Psoriasis and rheumatoid arthritis	3	5	2	2	0	3	7	2	0	5	5	2
8	Palindromic rheumatism	8	0	0	0	0	2	4	2	3	2	2	1
4	Still's disease	0	1	2	1	0	0	2	2	1	0	1	2
Total 263										180	52	20	11

Adapted in part from A.R.A. classification.[18]

**Grade:* *1—joint swelling, no joint destruction; 2—minimal cartilage or bone destruction; 3—subluxation; 4—ankylosis.*

***Class:* *1—asymptomatic, full activity; 2—minor symptoms, full activity; 3—moderate symptoms, light activity; 4—moderate-to-severe symptoms, light-to-no activity.*

†*Response:* *1—(excellent) asymptomatic; 2—(good) minor aches and pains; 3—(fair) slight persistence of joint tenderness and swelling; 4—(poor) moderate persistence or no relief of joint pain and swelling.*

Contraindications. Contraindications to the use of combined HN_2 and ACTH are similar to those discussed for HN_2 alone. In addition, the combination should not be used in a patient who has severe diabetes, infection, psychosis, advanced hypertension, or is allergic to ACTH.

Discussion

The combination of HN_2 and ACTH intravenously administered in a dose that for each drug was less than the usual dose when the drug is administered by itself, produced an effect that appeared to be synergistic, and resulted in an unusually low incidence of toxic reactions in a large number of patients with rheumatoid arthritis. The potentiating effect from the use of both agents occurred consistently and probably resulted from multiple-drug action rather than from an increase in one single pharmacologic action common to both agents.

In patients with various diseases, including carcinoma, lymphoma, arteritis or rheumatoid arthritis, treated with HN_2 or with combined ACTH and HN_2, it frequently was observed that the incidence of bone marrow depression depended not only on the dosage of HN_2 but also on the nature of the disease being treated. The hematopoietic system in patients with lymphoma or blood dyscrasia usually was more sensitive to HN_2 than that in patients receiving HN_2 for other diseases. Investigators [16,17] have shown that the effect on a normal hematopoietic system when HN_2 is used to suppress certain types of carcinoma is not clinically significant. We have noted a similar effect in patients with so-called collagen disorders.[9] Usually the effect of a small dose of HN_2 will be more noticeable on the inflammatory reaction involving the connective tissues than it will be on that involving the hematopoietic system. However, in patients with systemic lupus erythematosus, both the connective tissue and the hematopoietic system are sensitive to the effect of HN_2. In these patients, symptoms usually are suppressed by a total dose of 10 mg. of HN_2 in 2-mg. doses over a period of five days, combined with ACTH 10 units daily in 1 liter of 5 per cent dextrose in water. If symptoms are not adequately suppressed after one or two weeks, administration of one half of this amount of HN_2 and ACTH is repeated.

Combined ACTH and HN_2 has been particularly effective in acute and subacute rheumatoid arthritis, in acute and subacute systemic and disseminated lupus erythematosus, in palindromic rheumatism, and in hypercortisonism resulting from excessive use of corticosteroids. There was no clinical evidence of ill effects in those patients in whom it was used more than once within one year as treatment for exacerbations that were difficult to control. The indications for the administration of combined ACTH and HN_2 and the manner in which these drugs are utilized in the combined-drug program are discussed in part V.

II. INTRAARTICULAR ADMINISTRATION OF NITROGEN MUSTARD ALONE AND COMBINED WITH A CORTICOSTEROID FOR RHEUMATOID ARTHRITIS

Experimental and Clinical Studies

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DURING and after World War II extensive studies were made of the effects of HN_2 (nitrogen mustard) on various body tissues,[26] however no reports of its effects on synovial tissue have been encountered. Because of the observed suppressive action of intravenously administered HN_2 on acute joint inflammation of patients with rheumatoid arthritis (part I), it seemed worthwhile to study the effect of intraarticularly administered HN_2 on synovial tissue, both experimentally and clinically.

Experimental Study

Material and methods. Fifteen joints of seven healthy normal dogs were used in the study. Ten were injected with HN_2** alone, three with a combination of HN_2 and hydrocortisone tertiary-butylacetate (hereinafter termed *H.T.B.A.*), one with H.T.B.A. alone, and one was used as a control. Histologic examination was made of specimens of synovium obtained by open joint exploration, the dogs being sacrificed from 2 to 30 days after injection. Histologic specimens were fixed in Zenker's acetic acid fixing fluid (modified) and were stained with hematoxylin, eosin, and methylene blue. In the 14 experiments, the agent, dose, and time of examination were as follows:

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**HN_2 0.25 to 1.0 mg. dissolved in normal saline solution diluted to 1 mg. per milliliter.

Agent	Dose, mg.	Time of examination, no. of days after injection
HN_2	0.25	2
HN_2	0.25	4
HN_2	0.25	7
HN_2	0.50	2
HN_2	0.50	4
HN_2	0.50	7
HN_2	1.0	2
HN_2	1.0	4
HN_2	1.0	7
HN_2	1.0	30
HN_2	0.25	
H.T.B.A	25.0	4
HN_2	0.5	
H.T.B.A.	25.0	4
HN_2	1.0	
H.T.B.A.	25.0	4
H.T.B.A.	50.0	7

Results. During the period of observation before sacrifice, there was no evidence of pain on motion of any of the joints. All joints into which more than 0.25 mg. of HN_2 had been injected swelled slightly to moderately for from two to five days, after which time the swelling quickly subsided. Grossly the joints injected with HN_2 showed mild diffuse erythema of the synovium which was slightly greater in those areas having the heaviest concentration of HN_2. However, the synovial membrane examined 30 days after injection of HN_2 was normal in color, slightly irregular, and glistening.

The injection of HN_2 alone, produced changes in the synovialis that in general were histologically similar in all the joints; minor differences were interpreted as being the result of the differences in doses and in time intervals between the injections and the sacrifice of the animals. When a combination of HN_2 and H.T.B.A. was injected, the histologic changes were not so obvious; and when H.T.B.A. was injected alone, no significant histologic changes were apparent.

In the untreated synovial membrane from a normal dog there was observed a superficial layer of lining cells, with an underlying thin layer of collagen containing capillaries, on a fibroadipose stroma also containing capillaries (Fig. 1). Two days after intraarticular injection of 0.5 mg. of HN_2 there was absence of the superficial layer of lining cells and homogenization of the underlying superficial collagen (Fig. 2). A similar homogenization with endothelial swelling had occurred in the walls of some small blood vessels. Scanty lymphocytic infiltration was present superficially. Seven days after intraarticular injection of 1.0 mg. of HN_2 the changes were generally similar to those described for the two-day specimen with, in addition, a slight infiltration of histiocytes; again there was a slight or no inflammatory reaction. In certain areas there was beginning regeneration of the superficial layer of lining cells, which appeared as a thin, flat layer.

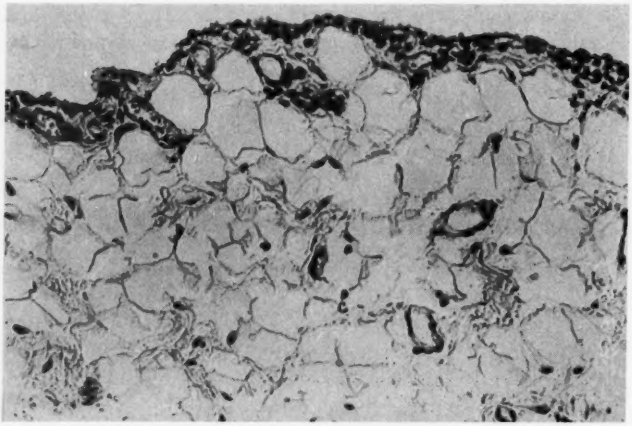


Fig. 1. Normal untreated canine synovial membrane. Hematoxylin-eosin-methylene blue; X225.

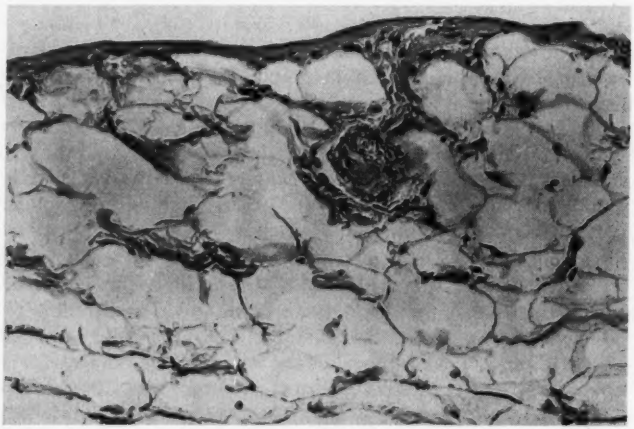


Fig. 2. Canine synovial membrane two days after intraarticular injection of 0.5 mg. of HN_2. Absence of layer of lining cells; homogenization of underlying collagen. Hematoxylin-eosin-methylene blue; X240.

Endothelial swelling in some areas had disappeared, and the walls of the blood vessel appeared to be almost normal. Thirty days after intraarticular injection of 1.0 mg. of HN_2 the synovial membrane appeared almost normal (Fig. 3); the collagen still showed faint alteration in staining character and was slightly homogenized. A mild lymphocytic and plasma-cell infiltration was present with fibroblastic proliferation in some superficial areas. H.T.B.A. administered alone caused no significant histologic changes; cellular infiltration and capillary and

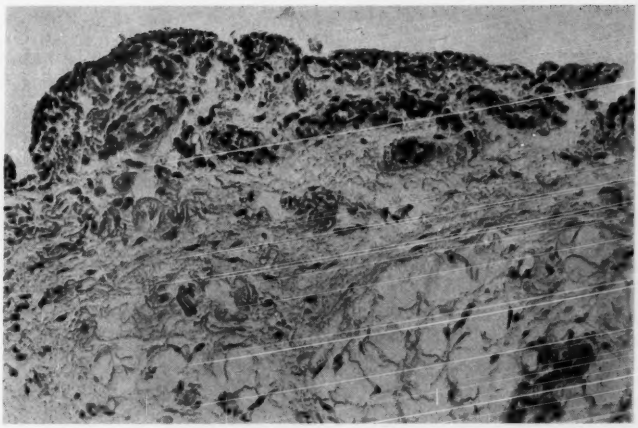


Fig. 3. Canine synovial membrane, almost normal, 30 days after intraarticular injection of 1.0 mg. HN_2. Hematoxylin-eosin-methylene blue; X160.

collagenous changes were absent (Fig. 4). A combination of 1 mg. HN_2 and 25 mg. H.T.B.A. caused only slight infiltration of lymphocytes, plasma cells, and histiocytes, with some capillary congestion and slight endothelial swelling; homogenization of underlying collagen and lysis of synovial membrane lining cells were not apparent (Fig. 5).

Summary. The injection of HN_2 into joints of normal dogs caused the following changes: (1) lysis and disappearance of the synovial membrane lining cells with subsequent regeneration of these cells; (2) transient fibrinoid change in underlying superficial collagen fibers, evidenced by homogenization and deep acidophilia in routinely stained hematoxylin-eosin sections, with greenish-blue streaks and smudges in the sections counterstained with methylene blue; (3) endothelial swelling in adjacent capillaries with congestion of the superficial vessels and focal extravasation of erythrocytes; (4) within 24 hours, scanty, focal, superficial infiltration with lymphocytes and plasma cells and an occasional neutrophil; later, infiltration with histiocytes which disappeared after a few weeks, and fibroblasts which persisted. The intraarticular administration of a combination of HN_2 and H.T.B.A. resulted in fewer histologic changes although slight swelling of synovial cells and endothelial cells was apparent. The fibrinoid change of collagen and lysis of synovial membrane lining cells were not observed in the three joints that were injected with a combination of the agents. H.T.B.A. administered alone caused no significant histologic change.

Fig. 4. Canine synovial membrane two days after intra-articular injection of hydrocortisone. There are no significant histologic changes; there is slight edema; cellular infiltration and capillary and collagenous changes are absent. Hematoxylin-cosin-methylene blue; X290.

Fig. 5. Canine synovial membrane four days after intra-articular injection of a combination of 1 mg. HN_2 and 0.25 mg. hydrocortisone. There are: slight infiltration by lymphocytes and plasma cells, an occasional histiocyte, congestion of capillaries, and slight endothelial swelling. The cells lining the synovial membrane are swollen but otherwise unaffected. Homogenization of the underlying collagen and lysis of synovial cells are not apparent. Hematoxylin-cosin-methylene blue; X290.

Clinical Study

Selection of patients and procedure. This study comprises a group of 130 patients with active rheumatoid arthritis who received intraarticular injections of HN_2 alone or in combination with hydrocortisone acetate or H.T.B.A. or prednisolone tertiary-butylacetate (hereinafter termed *P.T.B.A.*) over a period of two years. The duration and severity of the arthritis as well as the functional capacity of the patients varied widely. Thirty-three patients had grade 1, 42 patients had grade 2, 31 patients had grade 3, and 24 patients had grade 4 disease (A.R.A. classification modified[18]).

HN_2 alone was administered in 24 patients, 16 of whom had received no other medication for the arthritis and 8 of whom had taken medication orally, prior to the injections of HN_2, resulting in only partial relief of joint manifestations.

One hundred and six patients received HN_2 in combination with an intraarticular steroid; 28 of these patients had received no other medication for the rheumatoid arthritis and 78 were receiving medication orally which had resulted in only partial decrease in synovitis and swelling. In 28 of the latter 78 patients the medication consisted of iproniazid 12.5 mg. and prednisone 3 to 7.5 mg. daily; in 50 patients it consisted of prednisone 3 to 7.5 mg. daily and chloroquine phosphate 250 mg. daily or hydroxychloroquine sulfate 200 to 800 mg. daily. Forty-three of the 106 patients formerly had received three injections of H.T.B.A. alone, which usually had resulted in only temporary improvement of joint swelling lasting from 3 to 21 days following each injection.

Of the 106 patients, 50 were hospitalized and received three injections at three-day intervals. The 56 patients who were not hospitalized received three injections at 7 to 10 day intervals; and three to nine months later, 20 of these 56 patients received an additional two or three injections at 7 to 10 day intervals.

Drugs, dosages, and technic of intraarticular administration. Doses of HN_2 administered alone ranged from 0.1 to 1.0 mg.; those of 0.25 mg. or less were diluted in 0.5 ml. of saline solution, and those of 0.5 to 1.0 mg. were diluted in 1.0 to 2.0 ml. of saline solution. The combination of HN_2 and an intraarticular steroid was prepared as follows: 1 mg. HN_2 diluted in 1 ml. saline solution was mixed with hydrocortisone acetate, H.T.B.A., or P.T.B.A., 25 mg. per milliliter, in varying ratios for different joints.

Our technic for intraarticular injections, except into the wrist, was similar to that described by Hollander and associates.[27] The combination of HN_2 and an intraarticular steroid was used immediately after it was mixed, and promazine hydrochloride, 50 mg., was given orally before the injections inasmuch as nausea and vomiting occasionally occurred after as little as 0.5 mg. of HN_2, combined with intraarticular steroid, had been injected. The usual mixture for most joints was 0.5 mg. HN_2 in 0.5 ml. saline solution in 1 ml. (25 mg.) hydrocortisone acetate, H.T.B.A., or P.T.B.A. For elbow and ankle joints two injections, each containing 0.25 mg. of HN_2 combined with 0.5 ml. of an intraarticular steroid, was used. The wrist usually was injected in four areas: A, B, C, D (Fig. 6). The carpal tunnel, Area C, was injected routinely whenever there

was thickening or swelling of the transverse carpal ligament or restriction of wrist extension. The carpal tunnel was injected with 0.5 ml. (12.5 mg.) of an *intraarticular steroid alone* inasmuch as the median nerve which lies in the carpal tunnel should not be exposed to HN_2. The dorsal area of the wrist, Area A, was injected with 0.25 mg. of HN_2 diluted in 0.25 ml. of saline solution combined with 0.5 ml. of intraarticular steroid. One half of this amount in this combination was injected into the radial and ulnar regions, Areas B and D, when there was moderate or marked periarticular swelling. In order to reduce periarticular swelling in the wrist area, the latter injections were made into the deep subcutaneous tissue rather than into the joint space. The interphalangeal, metacarpophalangeal, and metatarsophalangeal joints were injected with doses of the combined drugs equivalent to those that were used in the radial and ulnar areas. The knees usually were injected with 0.5 mg. of HN_2 mixed with 1 ml. of intraarticular steroid, but when thick pannus formation or persistent effusion existed, the mixture was doubled to 1 mg. of HN_2 and 2 ml. of steroid. The hips, shoulders, and temporomandibular joints were injected only with steroid when an intraarticular injection appeared warranted.

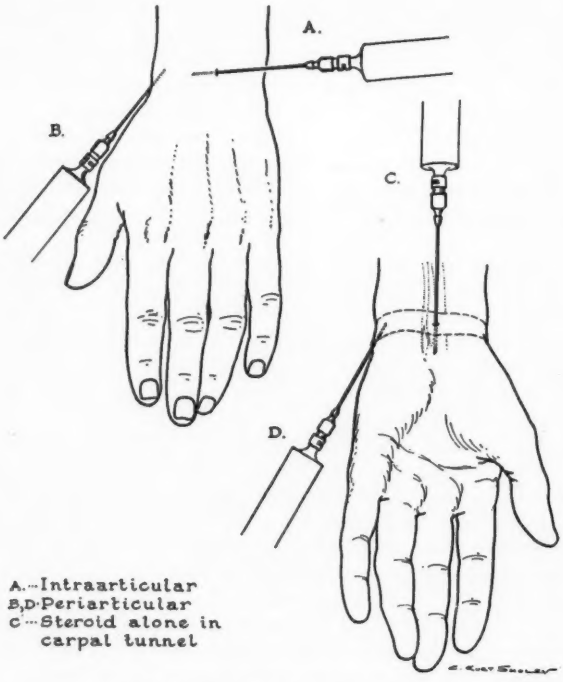


Fig. 6. Technic for injecting the wrist.

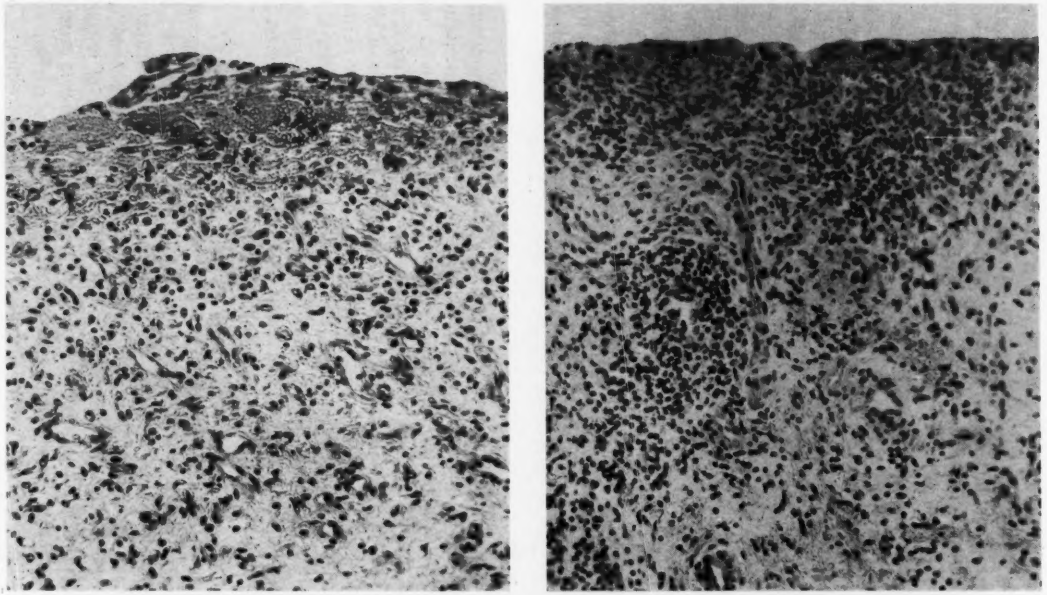
Results. Of the 24 patients receiving HN_2 alone, 18 had a marked decrease in synovitis. However, it was observed that while a rapid and prolonged decrease in joint swelling occurred after the injection of HN_2 alone, pain was not relieved so readily or so completely as it was after the injection of intra-articular steroid. Therefore, 106 patients in this study, and all subsequent patients receiving intraarticular injections of HN_2, also received intraarticular steroid. The rationale of combining the drugs was to prolong the desirable but temporary effect obtained when intraarticular steroid was used alone.

In 37 of the 106 patients with persistent synovial inflammation and thickening present for from one year to eight years, who received combined HN_2 and intraarticular steroid there was complete disappearance of pain and swelling. These 37 patients now have been observed for 18 to 24 months and there has as yet been no recurrence of pain, swelling, or tenderness of the previously involved joints. In 35 of the remaining 69 patients, joint swelling was absent for six to nine months, after which time it recurred but to a lesser degree and was again suppressed by one or two additional injections. Pain subsided completely in 20 and incompletely in 15 of these 35 patients. Of the 34 remaining patients, in 24 there was incomplete disappearance of pain and swelling and in 10 there was no significant response to treatment.

In 28 of the 34 patients who responded poorly to the combined therapy, extensive fibrosis, cartilage destruction, relaxation of ligaments, and painful crepitation were prominent before treatment. Aggravation of joint instability frequently occurred after a joint with relaxed ligaments had decreased in size as a result of treatment.

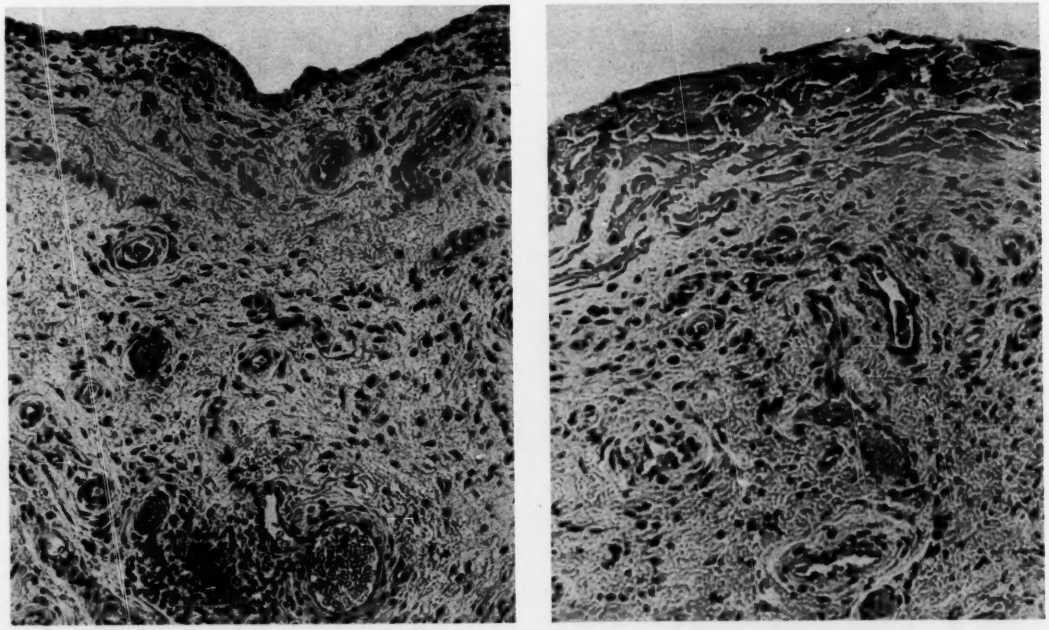
Twenty-six patients who for more than one year had persistent swelling of one or more large joints, associated with increased erythrocyte sedimentation rates and serum polysaccharide-protein ratios, and who had received oral medication for six months or more without significant relief of joint manifestations, were given as supplemental therapy three intraarticular injections of HN_2 and H.T.B.A. into each of the involved joints. In addition to further clinical improvement manifested by decrease in joint swelling there was return to normal of the erythrocyte sedimentation rates and serum polysaccharide-protein ratios. In each instance it appeared that disease activity had been altered by intraarticular administration of HN_2.

Toxicity and sensitivity reactions. There was no evidence of hematopoietic depression following the administration of this small amount of HN_2. In 33 patients serial roentgenograms of joints one year after the initial injections of HN_2 have shown no evidence of injury to cartilage or bone. In one patient the HN_2 was not injected completely into the joint, and a small area of painless induration developed along the site of the needle tract, which became crusted and disappeared spontaneously within three months. Frequently nausea and occasionally vomiting occurred within one to four hours after administration of as little as 0.5 mg. of HN_2; these symptoms were satisfactorily controlled when 50 mg. of promazine hydrochloride was given orally before the injection of HN_2. In 10 patients localized itching associated with a temporary increase



(a) (b)

Fig. 7. Human synovial membrane, acute rheumatoid arthritis, before treatment. (**a**) A few epithelial-like lining cells are present. Fibrin deposition, granulation tissue, slight infiltration by neutrophils and slight superficial edema and congestion are present. Hematoxylin-eosin-methylene blue; X200. (**b**) Epithelial-like lining cells are absent; marked neutrophil infiltration is present with occasional lymphocytes and plasma cells. A focal collection of lymphocytes and histiocytes is present around a capillary. Hematoxylin-eosin-methylene blue; X200.



(a) (b)

Fig. 8. Human synovial membrane, acute rheumatoid arthritis, one month after intraarticular HN_2. (**a**) Synovial lining cells are present. Focal lymphocyte and plasma cell infiltration and congestion of capillaries are evident. Hematoxylin-eosin-methylene blue; X185. (**b**) Homogenized fibrin superficially, and rare lymphocyte and plasma cell present. Hematoxylin-eosin-methylene blue; X225.

in joint swelling, and a maculopapular erythematous rash developed directly over the injected joint a few hours after the injection and usually lasted for from 24 to 72 hours. In 12 patients who had received a combination of HN_2 and H.T.B.A. or P.T.B.A., an increase in joint swelling persisted for one or two weeks and then suddenly subsided. It is not known whether this swelling resulted from a sensitivity reaction to medication, or from temporary irritation of the synovial membrane.

Histologic features of synovial membrane. The effect of HN_2 in small doses administered intraarticularly is illustrated by the comparison of microscopic sections of synovial membrane before and after treatment (Figs. 7 and 8). A 26-year-old married woman having persistent rheumatoid arthritis of one year's duration developed an acute exacerbation. Both knees were swollen, warm, and painful on motion. Open biopsy was performed to obtain synovial membrane from the left knee. The following day 1 mg. of HN_2 diluted in 1 ml. of normal saline solution was injected intraarticularly, and thereafter every third day for a total of three injections. No other medication was given, and a repeat open biopsy was performed at the same site one month later.

A specimen of synovial membrane obtained before treatment showed microscopically an acute synovitis evidenced by focal absence of the epthelial-like layer of lining cells, superficial fibrin deposition, massive infiltration of neutrophils, a few foci of lymphocytes, a few plasma cells, histiocytes, granulation tissue, slight fibrosis, edema and congestion (Fig. 7).

Synovial membrane obtained from a comparable site from the same patient one month after treatment with HN_2 showed a small amount of fibrin, homogenized in part, the epithelial-like lining cells present except over the fibrinous areas, rare focal collections of lymphocytes and plasma cells, and congestion of capillaries. Neutrophils had almost completely disappeared (Fig. 8).

Discussion

The intraarticular administration of HN_2 has been used primarily as a supplement to the administration of intraarticular steroid in selected cases heretofore resistant to treatment but still potentially reversible. With the technic and dosage described, side effects were insignificant, and continued use of both agents did not appear to be harmful.

The local action of HN_2, as described above, appears to cause marked reduction in the inflammatory reaction as evidenced by a decrease in cellular exudate and edema. In addition there were alterations in the synovial membrane lining cells resulting in eventual regeneration. There was a lack of inflammatory response when HN_2, was injected into the joints of dogs, whereas when an equivalent dose of HN_2 was injected into the muscles of dogs, local inflammatory response occurred, histologically manifested by diffuse infiltration

of neutrophils, principally around blood vessels and degenerated muscle fibers (Fig. 9).

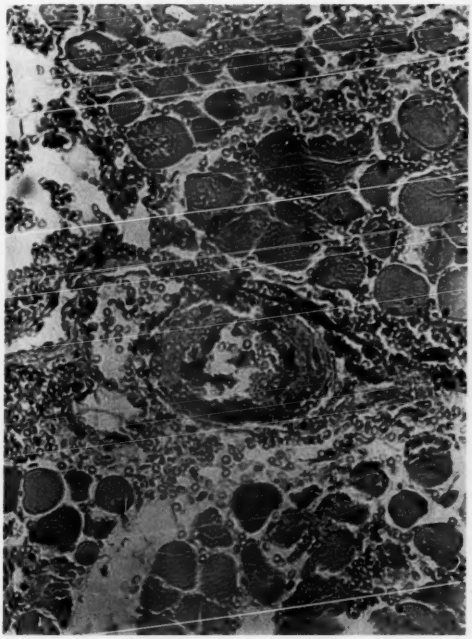


Fig. 9. Canine muscle two days after injection of HN_2. Cellular infiltration (neutrophils) in area of hemorrhage; homogenization of vessel wall. Some muscle fibers were degenerated. Hematoxylin-eosin-methylene blue; X240.

The intraarticular injection of H.T.B.A. or a related steroid and HN_2 in most patients having advanced joint disease not infrequently resulted in rapid and significant reduction in joint size but also in an unstable joint because of relaxed ligaments, atrophy of adjacent muscle, and destruction of cartilage. In many instances these patients had rather severe anxiety reactions and were fearful of increasing their exercise lest joint swelling recur. It is questionable that they were actually benefited by treatment.

At the present time we believe that HN_2 can be safely and effectively administered intraarticularly alone or in combination with H.T.B.A. or P.T.B.A. for suppression of persistent rheumatoid synovitis with or without effusion of joints. It is used mainly as a supplement to other therapeutic agents that then may be given in smaller doses in an attempt to continue the suppression of disease activity. Temporary side effects, clinically insignificant, may occur, but no serious or harmful effects of HN_2 have been noted during a two-year follow-up. However, there must be long-term observation before this form of therapy can be fully evaluated.

III. THE EFFECT OF ISONIAZID AND OF IPRONIAZID IN PATIENTS WITH RHEUMATOID ARTHRITIS

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DEPRESSION, exhaustion, anxiety, conversion, and other emotional reactions characteristically accompany chronic debilitating diseases and may limit the patients' recovery from their primary disease or even prevent satisfactory improvement. To many of these patients the desirable effects that result from the administration of the hydrazides, especially iproniazid, include a generalized sense of well-being, increase in appetite, gain in weight, and decrease in fatigability. However, constipation, lightheadedness, postural hypotension, dysuria, loss of libido, muscular irritability, hyperactivity of deep reflexes, paresthesia, nervousness, excessive dreaming, and insomnia may also occur.[28] At times, an increase in the frequency and the severity of convulsions occurs in epileptics, and psychotic episodes develop in predisposed patients.[29] Discontinuation of the hydrazides after prolonged administration is at times associated with irritability, restlessness, excessive dreaming, headache, vertigo, and nausea. This "withdrawal syndrome" is observed more frequently after discontinuation of iproniazid than after isoniazid therapy. It usually appears within 24 to 48 hours after cessation of therapy and persists with gradual regression for approximately 10 to 14 days. Occasionally, vitamin-B deficiency syndromes occur, suggesting that under certain conditions these drugs may compete in the body with nicotinic acid.[30] Today, most authorities believe that isoniazid is a safe drug for long-term usage but that iproniazid, in the dosage of 300 mg. daily used for the treatment of tuberculosis, too frequently produces toxic reactions. The mechanism of the action responsible for the effects of the hydrazides is not known, but it probably is related to an alteration in enzyme systems that affect certain components of the autonomic nervous system.[31]

In June 1952 we began to investigate the effect of the hydrazides on subjective and objective manifestations in patients with rheumatoid arthritis. It is widely known that there often is a lack of correlation between the patient's symptoms and the degree of disease activity as determined objectively. Many patients with active rheumatoid arthritis display emotional immaturity, depression, hostility, and dependency; the degrees of disturbance vary among the patients. Anorexia associated with loss in weight may be a serious problem, and fatigability may limit even a modest amount of activity. When these symptoms predominate, a low pain threshold usually is present. In evaluating the effect of isoniazid and iproniazid in a group of patients with active rheumatoid arthritis, we considered both the emotional disturbance and the objective disease manifestations.

Methods

Seventy-four adults having active rheumatoid arthritis of varying severity of from 1 to 12 years' duration were treated with isoniazid or iproniazid and were followed for two to five years. Forty-four patients (20 of whom were hospitalized) initially received isoniazid orally, 100 mg. three times daily; and 30 (21 of whom were hospitalized) initially received iproniazid orally, 50 mg. three times daily for from one to three months, after which time the dosage was gradually reduced to 25 mg. daily or every other day. Each of the 74 patients also received from 10 to 25 mg. of pyridoxine (vitamin B_6)daily in order to prevent peripheral neuritis.[30]

Forty-one patients were hospitalized initially for treatment, and during hospitalization, bed rest, physiotherapy, and aspirin from 4 to 6 gm. daily, supplemented the administration of the hydrazide. The other 33 patients were outpatients during the entire course of treatment.

All patients were seen at one- or two-month intervals during a two-year period, and more than half of the patients still are under observation and return for examination at three-month intervals. Complete blood counts and routine urinalyses were obtained at weekly intervals for the first month and at monthly intervals for one year, after which time they were obtained at three-month intervals. Sedimentation rates, serum polysaccharide-protein ratios, and electrophoretic patterns of plasma proteins were determined at monthly intervals for 12 to 18 months. Bromsulphalein excretion and serum bilirubin values were determined at two-month intervals. Urea clearance was tested at three-month intervals.

After one year of treatment with the hydrazides, those patients who had not improved satisfactorily then were given a combination of a hydrazide and a corticosteroid in dosages that by themselves were insufficient to suppress disease activity.

Results

Alterations in affect. In patients receiving isoniazid, improvement in symptoms was slow and undramatic; whereas, in those receiving iproniazid, significant improvement occurred within 3 to 10 days.

In patients receiving iproniazid the first response was a gradual increase in their generalized sense of well-being. Patients who formerly were depressed began to smile faintly, to show interest in their immediate surroundings, and presently to note an improvement in appetite. Many patients commented that they were beginning to feel as they had felt before they developed rheumatoid arthritis. Although joint pain and swelling still were present, these joint manifestations appeared to be tolerated better and were less cause for concern than they had been; most of the hospitalized patients began to use their joints more and noted a generalized increase in strength. However, as these subjective

changes occurred, there was little or no objective change in the involved joints that could not be explained on the basis of bed rest or of physiotherapy.

Objective response. A gain in weight was the most consistent objective response to hydrazide therapy; it occurred in 10 of the 44 patients receiving isoniazid and in 26 of the 30 patients receiving iproniazid. Increases ranged from 3 to 24 pounds during the first month of treatment and then usually tapered sharply; however, eight patients continued to gain weight and eventually their obesity became a problem.

Before treatment the temperature was elevated above 100 degrees F. in 30 patients (11 subsequently received isoniazid and 19 iproniazid) who were hospitalized. In 21 of these patients (6 receiving isoniazid and 15 receiving iproniazid) it returned to normal within three weeks.

Objective improvement in the joint manifestations was not consistent in either group. Only 10 of the 44 patients who received isoniazid had significant relief of joint manifestations after six months, and 20 of the remaining 34 were given supplemental doses of cortisone after one year because of an unsatisfactory response to treatment. During the first three weeks joint swelling and tenderness on pressure subsided in 9 of 21 hospitalized patients receiving iproniazid. In seven additional patients receiving iproniazid there was partial relief of inflammation after five weeks. Joint manifestations had subsided completely in 20 of 30 patients receiving iproniazid after six months and in an additional three patients after one year.

Laboratory findings. Isoniazid caused no significant change in the hemoglobin content, red blood cell count, white blood cell count, or differential cell count. Urinalyses revealed no abnormalities. Erythrocyte sedimentation rates became normal in 2 patients, and were decreased 50 per cent or more in 18 patients. The serum polysaccharide-protein ratios decreased in 26 of the 44 patients.

In 16 of the 30 patients receiving iproniazid, there was a decrease of 1 to 2 gm. in hemoglobin content during the first month of therapy. In 10 of these patients the hemoglobin content increased to the original value or exceeded it during the subsequent six months. No changes were noted in peripheral white blood cell counts or in urinalyses. The sedimentation rates fell to normal within six months in eight patients, and were decreased 50 per cent or more in five patients. The serum polysaccharide-protein ratios decreased in 22 of the 30 patients.

Side effects and toxicity reactions. It soon became obvious that the desirable subjective improvement resulting from the hydrazides was intimately associated with the effects on the central, autonomic, and peripheral nervous systems. These included constipation, loss of libido, lightheadedness, postural hypotension, blurring of vision, hyperactivity of deep tendon reflexes, and clonus. Symptoms were most prevalent when iproniazid had been given in doses of 150 mg. daily for two or three months. Palms that had been cold and moist became warm and dry, and within a few months palmar erythema appeared in 20 of the 44 patients receiving isoniazid and in 16 of the 30 patients receiving

iproniazid. Deep tendon reflexes became hyperactive between the second and third month of therapy in 20 patients receiving 300 mg. or more of isoniazid, and in all patients receiving 75 mg. or more of iproniazid. The hyperactivity was more pronounced in those patients receiving iproniazid, and usually was accompanied by mild muscular irritability manifested by coarse fascicular muscular contractions and spasms that usually were noted when the patient was in a relaxed state, especially while in bed before going to sleep. Through experience it was learned that hyperactivity was an indication that the drug immediately should be reduced in dosage or should be temporarily discontinued.

Five patients receiving iproniazid, 150 mg. daily for three months, developed clonus; three had mild clonus and two had severe generalized clonus with marked postural hypotension and hyperexcitability which persisted for two or three days after administration of the drug had been stopped. In the two patients having severe generalized clonus all joint manifestations disappeared, but they reappeared when the hyperactive state had subsided a few weeks later. In all five patients while clonus was present, plasma cholinesterase (pseudocholinesterase) levels were greatly decreased, but increased as signs of toxicity disappeared. It is interesting that cholinesterase levels also are decreased during pregnancy[32] when rheumatoid arthritis frequently improves. Bromsulphalein excretion was temporarily impaired in three of these patients: retention ranged from 20 to 27 per cent for two or three months. Serum bilirubin values remained normal. After the toxic manifestations had disappeared, administration of iproniazid, 25 mg. on alternate days, was resumed without ill effect in each of the five patients. Withdrawal symptoms manifested by headache, irritability, and excessive dreaming occurred in three of these five patients after administration of iproniazid was abruptly discontinued. These symptoms subsided after from three to six days.

Uncommon side effects. Four patients developed a maculopapular skin eruption within one month after beginning isoniazid therapy. In all four the dermatitis disappeared when the drug was stopped and iproniazid was substituted. One 37-year-old woman after two months of isoniazid therapy developed rather severe edema of the entire body. No cause was found, but the edema disappeared when the drug was stopped. Two patients developed jaundice, believed to be due to toxic hepatitis; both had proved mild cirrhosis before isoniazid was administered. One patient had biliary cirrhosis at the time a cholecystectomy was performed before isoniazid was started. The other patient had a long history of excessive drinking of alcoholic beverages when he developed rheumatoid arthritis; at the time that the jaundice occurred, a liver biopsy confirmed the diagnosis of portal cirrhosis. Both patients recovered uneventfully from the toxic hepatitis.

The incidence of peripheral neuropathy in patients who received either isoniazid or iproniazid alone or in combination with other drugs was 0.7 per cent. In each instance administration of the drug was stopped and 30 mg. of pyridoxine daily was administered; hyperesthesias and paresthesias disappeared within approximately four weeks.

Effect of a Combination of a Hydrazide and a Corticosteroid

The next step in our study led to supplementing the hydrazides with corticosteroids in dosages that in themselves were insufficient to suppress rheumatoid activity satisfactorily.

Methods. One hundred and one patients having active rheumatoid arthritis of varying severity and duration received one of the hydrazides and one of the corticosteroids. The patients were grouped as follows (Table 1): *group 1*—47 patients, isoniazid and cortisone; *group 2*—20 patients, isoniazid and prednisone; *group 3*—20 patients, iproniazid and cortisone; *group 4*—14 patients, iproniazid and prednisone. Twenty of the 47 patients in group 1, initially received isoniazid alone for one year, during which time response to therapy was considered unsatisfactory. All patients were examined at one- or two-month intervals for one year or more.

Results. All patients with relatively early or nonprogressive disease (grade 1) responded satisfactorily to therapy utilizing any combination of a hydrazide and a corticosteroid (Table 1). However, patients with more advanced disease (grades 2, 3, 4) did not respond so completely or so consistently to the combination of isoniazid and cortisone in the doses used, as those patients who received isoniazid and prednisone, iproniazid and cortisone, or iproniazid and prednisone. Of the 20 patients with grade 2 disease receiving isoniazid and cortisone, only 7 became asymptomatic, as compared to 6 of the 7 patients receiving isoniazid and prednisone. All patients with grade 2 rheumatoid arthritis receiving iproniazid and either cortisone or prednisone became asymptomatic within one year after starting medication. As a group, the 20 patients with grades 3 and 4 rheumatoid arthritis who were receiving isoniazid and cortisone responded unsatisfactorily, inasmuch as only 1 patient became asymptomatic and 14 had a poor response to therapy. Of the 15 patients having grades 3 or 4 rheumatoid arthritis who were receiving iproniazid and either cortisone or prednisone, 5 became asymptomatic while 4 did not improve significantly during the same period of time. These findings suggest that the corticosteroid was the primary drug responsible for the relief of joint manifestations and that prednisone was more effective than cortisone. However, the combination of iproniazid and cortisone appeared to be as effective in relieving joint manifestations as any of the other combinations of a hydrazide and a corticosteroid.

The majority of patients receiving any combination of these drugs gained weight and developed moon facies, plethora, and supraclavicular fat pads, despite the relatively small doses of corticosteroid that were used. Approximately one third of the younger women developed menstrual irregularities after six months of therapy: menses occurred more frequently, and occasionally there was menorrhagia that ceased when the medication was discontinued.

Contraindications. The hydrazides appear to be safe to use in the dosages recommended. However, they are contraindicated in patients having hepatic disease, severe anxiety states, epilepsy, and alcoholism.

Table 1.—*Results of combined hydrazide-corticosteroid therapy for rheumatoid arthritis in 101 patients*

Group no.	No. of patients	Grade*	Class** (No. of patients) 1	2	3	4	Duration of disease in years	Drug combination	Response† after 2 years of treatment (No. of patients) Good	Fair	Poor
1	7	1	1	3	3	0	1 to 3	Isoniazid, 100 mg. t.i.d.	6	1	0
	20	2	0	10	8	2	1 to 7	Cortisone, 12.5 mg. t.i.d.	7	10	3
	14	3	0	4	8	2	1 to 12		1	4	9
	6	4	0	2	3	1	1 to 16		0	1	5
Total	47		1	19	22	5			14(30%)	16	17
2	4	1	0	3	1	0	1 to 2	Isoniazid, 100 mg. t.i.d.	4	0	0
	7	2	0	2	3	2	1 to 8	Prednisone, 1.0 to 2.5 mg. t.i.d.	6	1	0
	6	3	0	1	4	1	2 to 6		2	2	2
	3	4	1	0	1	1	3 to 10		0	1	2
Total	20		1	6	9	4			12(60%)	4	4
3	5	1	0	2	3	0	1 to 2	Iproniazid, 10 to 25 mg. daily	5	0	0
	6	2	0	2	4	0	1 to 6	Cortisone, 12.5 mg. t.i.d.	6	0	0
	4	3	0	2	2	0	3 to 7		3	1	0
	5	4	0	2	0	3	3 to 10		1	2	2
Total	20		0	8	9	3			15(75%)	3	2
4	4	1	0	2	2	0	1 to 3	Iproniazid, 10 to 25 mg. daily	4	0	0
	4	2	0	2	2	0	1 to 12		4	0	0
	4	3	1	1	1	1	1 to 6	Prednisone, 1.0 to 2.5 mg. t.i.d.	1	2	1
	2	4	0	1	1	0	4 to 8		0	1	1
Total	14		1	6	6	1			9(64%)	3	2
Total	101		3	39	46	13			50(50%)	26	25

Adapted in part from A.R.A. classification.[18]

**Grade:* *1—joint swelling, no joint destruction; 2—minimal cartilage or bone destruction; 3—subluxation; 4—ankylosis.*

***Class:* *1—asymptomatic, full activity; 2—minor symptoms, full activity; 3—moderate symptoms, light activity; 4—moderate-to-severe symptoms, light-to-no activity.*

†*Response:* *Good—no symptoms, full activity; Fair—mild-to-moderate symptoms, full activity; Poor—moderate-to-severe symptoms, limited activity.*

Comment

It was concluded from this study that the hydrazides had little effect on objective joint manifestations. However, improvement of affect occurred when there was depressed psychomotor activity, leading us to believe that the treatment may cause midbrain stimulation which, if carefully controlled, is desirable in these patients. Iproniazid was more effective than isoniazid and we found it to be a safe drug for long-term use when properly administered. The dosage of iproniazid ranged from 50 to 150 mg. daily for the first week and then was gradually reduced at weekly intervals over a period of two or three weeks. The maintenance dose was determined by administering a sufficient amount of iproniazid to elevate mood and yet not result in marked hyperactivity of the deep reflexes. The potentially cumulative action of iproniazid always was considered when dosage increases were necessary for short periods of time. When the deep reflexes reacted briskly without clonus, the dosage of iproniazid was further reduced to and maintained at 10 to 15 mg. daily. This small dosage of iproniazid has been sufficient to maintain the desirable mental stimulation that is initially produced by a larger dosage. When the dosage of iproniazid was individualized as described, it could be used for prolonged therapy without the occurrence of toxic reactions; withdrawal symptoms did not occur when the drug was stopped.

The favorable effects of the hydrazides, especially iproniazid, on subjective manifestations in patients with rheumatoid arthritis were the most interesting and perhaps the most significant findings of this study. The mechanism of action is not known, but it probably is related to alteration of enzyme systems. We believe that multiple alterations in enzyme systems, rather than inhibition of monoamine oxidase by itself, are responsible for the numerous effects observed in various connective tissue diseases. We have observed inhibition of plasma cholinesterase in patients who had toxic reactions due to overdosage of hydrazides. When clinical signs of toxicity were apparent, liver function was temporarily depressed, as manifested by delayed excretion of Bromsulphalein. It was not determined from our studies whether the decrease in plasma cholinesterase was due to a specific action of the hydrazide or was a secondary manifestation related to temporary depression of liver function. In addition, palmar erythema usually appeared three to six months after the hydrazide had been started. It is possible that there was impaired inactivation of estrogen by the liver. Inhibition of liver function has been observed also by Wiesel and his group,[33] who reported a delay in hepatic inactivation of cortisone and related compounds. However, they believe that the therapeutic activity of cortisone seems to increase without at the same time producing the undesirable side reactions noted with doses of cortisone large enough in themselves to produce an equal degree of anti-inflammatory activity. In our studies we were unable to confirm this observation and we believe that the toxic side effects of cortisone increased in proportion to the increased therapeutic activity obtained with a relatively small dose of cortisone. No advantage was noted in using the combination of isoniazid and cortisone to obtain this effect since the advent of the newer more powerful corticosteroids.

We also have observed a direct stimulating action on the healing of small ischemic ulcers frequently seen at the tips of the fingers and over the dorsum of the interphalangeal joints in patients with scleroderma and systemic lupus erythematosus, especially when the drug was applied locally in the form of a 3 to 5 per cent iproniazid ointment in a lanolin or petrolatum base.

Conclusion

In patients with rheumatoid arthritis and certain other connective tissue diseases, the hydrazides appear to have multiple unrelated effects that probably result from alterations in certain enzyme systems. Inhibition of monoamine oxidase and cholinesterase has been observed. The utilization of pyridoxine is increased; this vitamin is essential in the enzyme systems that decarboxylate many amino acids, and influences the metabolism of tryptophane. Clinically the hydrazides exert a stimulating effect on the central and autonomic nervous systems, and occasionally may produce a peripheral neuropathy. They have a depressing effect on liver function, and a local stimulating action on the healing of tissues.

IV. COMPARISON OF EFFECTS OF TWO ANTIMALARIAL AGENTS, HYDROXYCHLOROQUINE SULFATE AND CHLOROQUINE PHOSPHATE, IN PATIENTS WITH RHEUMATOID ARTHRITIS

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SOME of the antimalarial agents that have a valuable anti-inflammatory action in patients having discoid or systemic lupus erythematosus have been found to have a similar effect in patients having rheumatoid arthritis.[34,35] However, these drugs have not been used widely for rheumatoid arthritis because of their undesirable side effects.

The first antimalarial agent used in the treatment of discoid lupus erythematosus was quinacrine hydrochloride*, an acridine derivative,[36] but the undesirable side effects of this drug often were serious and sometimes fatal; they included nausea, anorexia, vomiting, dermatitis, nervousness, insomnia, headache, blurring of vision, agranulocytosis, and aplastic anemia. Primaquine diphosphate**, an 8-aminoquinoline, also was found to have anti-inflammatory activity, but its side effects, as reported by Steck and his group,[37] prevented its widespread clinical use. They found methemoglobinemia and pallor in all, anorexia in 14, and leukopenia in 7 of 21 patients having rheumatoid arthritis who were given the drug for two weeks.

Chloroquine phosphate, a 4-aminoquinoline, has been reported to be effective in the treatment of both systemic lupus erythematosus and rheumatoid arthritis. Dubois and Martel[38] believe that chloroquine phosphate is as effective as quinacrine hydrochloride in the treatment of moderately active systemic lupus erythematosus. Freedman[39] reported the effect in 50 patients with rheumatoid arthritis who received 300 mg. of chloroquine sulfate daily for two years. Apparently 43 patients became entirely or nearly asymptomatic, although some continued to have elevated sedimentation rates, which indicated that disease activity persisted. Of the other seven patients, three continued to have slight joint inflammation and four failed to show satisfactory response to the drug. No significant toxic effects were noted in any of the 50 patients. Freedman believed that the results of his study warranted a larger investigation.

**Atabrine hydrochloride, Winthrop Laboratories.*

***Primaquine diphosphate, Parke, Davis & Co.*

In 1950 hydroxychloroquine sulfate, a new 4-aminoquinoline, was introduced as an antimalarial drug that potentially has a high degree of clinical safety and effectiveness. Reports [40-42] substantiate its efficacy in the management both of discoid and of systemic lupus erythematosus, and its relatively nontoxic influence. To date toxic reactions are reported as being few and not serious.[40,43]

It is the purpose of our report to describe the effects of hydroxychloroquine sulfate in patients with active rheumatoid arthritis, and to compare these effects with those in a similar group of patients who received chloroquine phosphate for 18 months.

Methods

Forty-five patients having active rheumatoid arthritis of varying severity of 15 months' to 26 years' duration received oral antimalarial therapy; results were evaluated after 18 months. Twenty-six patients were given hydroxychloroquine sulfate in doses of from 200 to 600 mg. daily. When improvement occurred the dose was reduced to one half of what they had been receiving. Ten of the 26 patients were hospitalized for treatment. Twenty-five patients received chloroquine phosphate. Initially the dosage was 0.5 gm. daily; when improvement occurred, usually within six to eight weeks, the dose was reduced to 0.25 gm. Eight of the 25 patients were hospitalized for treatment. Hospitalized patients in both groups received daily physiotherapy, and sodium salicylate, 1-gm. doses four times daily for the relief of pain.

Results

Clinical status after 18 months (Tables 1, 2). In the group of 26 patients who were receiving hydroxychloroquine sulfate, 15 patients were asymptomatic, 5 patients showed significant improvement, and 6 patients had unsatisfactory results (3 could not tolerate the medication, which had to be stopped after a few days, and 3 were considered 'drug failures' showing grade 4 improvement after from six to nine months of therapy).

The 25 patients who were receiving chloroquine phosphate could be classed nearly equally into three groups: Nine patients were asymptomatic, eight showed moderate improvement, and eight had unsatisfactory results (six could not tolerate the medication, which had to be stopped after a few days or weeks, and two were considered 'drug failures').

Improvement never was dramatic and usually began between the third day and the fourth week. The first sign of improvement usually was a decrease in joint pain, followed by a decrease in the gel reaction. Acute joint inflammation often persisted for 10 days or longer after therapy had been started; effusions disappeared slowly and at times incompletely. Muscular strength returned to normal in 11 and improved significantly in 4 of 18 patients who had muscular

Table 1.—*Comparison after 18 months of the effect of hydroxychloroquine sulfate and of chloroquine phosphate in patients with rheumatoid arthritis*

Drug	Number of patients	Grade* of disease	Class**				Duration of disease	Response† after 18 months			
			1	2	3	4		1	2	3	4
			No. of patients					No. of patients			
Hydroxychloroquine sulfate	7	1	0	2	3	2	16 mo. to 2 yr.	3	2	1	1
	10	2	0	5	5	0	19 mo. to 4 yr.	5	2	1	2
	5	3	0	1	3	1	3 yr. to 12 yr.	0	2	2	1
	4	4	0	1	2	1	3 yr. to 18 yr.	0	1	1	2
Total	26		0	9	13	4		8	7	5	6
Chloroquine phosphate	6	1	0	3	2	1	15 mo. to 3 yr.	2	1	1	2
	6	2	0	4	2	0	17 mo. to 8 yr.	1	1	3	1
	8	3	0	2	5	1	2 yr. to 15 yr.	1	1	3	3
	5	4	0	1	3	1	3 yr. to 26 yr.	0	2	1	2
Total	25		0	10	12	3		4	5	8	8

Adapted in part from A.R.A. classification.[18]

**Grade of disease: 1—joint swelling; 2—early cartilage or bone destruction; 3—subluxation; 4—ankylosis.*

***Class: 1—no symptoms with full activity; 2—minor symptoms with full activity; 3—moderate-to-severe symptoms with restricted activity; 4—moderate-to-severe symptoms at rest.*

†*Response: 1—asymptomatic, normal sedimentation rate and serum polysaccharide-protein ratio; 2—asymptomatic, abnormal sedimentation rate and serum polysaccharide-protein ratio; 3—significant improvement with minor joint manifestations; 4—minor improvement with significant joint manifestations.*

Table 2.—*Summary of results after 18 months of treatment with hydroxychloroquine sulfate*

4 = minor improvement with significant joint manifestations.

Table 2. — *Summary of results after 18 months of treatment with hydroxychloroquine sulfate or with chloroquine phosphate in patients with rheumatoid arthritis*

Grade of disease (See Table 1.)	Results* in 26 patients treated with hydroxychloroquine sulfate	Results** in 25 patients treated with chloroquine phosphate
1	**7 patients:** Of 6 patients able to tolerate drug, 5 were asymptomatic, 1 had minor symptoms. Drug was stopped in 1 patient because of gastrointestinal distress.	**6 patients:** Of 4 patients able to tolerate drug, 3 were asymptomatic, 1 had minor symptoms. Drug was stopped in 2 patients: 1 because of skin reaction, 1 because of gastrointestinal distress.
2	**10 patients:** Of 9 patients able to tolerate drug, 7 were asymptomatic, 1 had significant improvement, 1 had minor or grade 4 improvement. Dose was reduced in 1 patient and drug was stopped in 1 patient because of gastrointestinal distress.	**6 patients:** Of 5 patients able to tolerate drug, all were asymptomatic sometime during 18 months, but 3 developed additional joint manifestations after six months. Dose was reduced in 2 patients: 1 because of gastrointestinal distress, 1 because of tinnitus. Drug was stopped in 1 patient because of gastrointestinal distress.
3	**5 patients:** Of 4 patients able to tolerate drug, 2 were asymptomatic and 2 had significant improvement. Dose was reduced in 1 patient because of gastrointestinal distress. Drug was stopped in 1 patient because of maculopapular rash with local exfoliation.	**8 patients:** Of 6 patients able to tolerate drug, 2 were asymptomatic, 3 had significant improvement, 1 had minor or grade 4 improvement. Dose was reduced in 5 patients: 3 because of mild gastrointestinal distress, 2 because of nervousness. Drug was stopped in 2 patients: 1 because of dermatitis, 1 because of gastrointestinal distress.
4	**4 patients:** Of 4 patients able to tolerate drug, 1 patient was asymptomatic, 1 had significant improvement, 2 patients had minor or grade 4 improvement. Dose was reduced in 1 patient because of nervousness and slight mental confusion which subsided after first week of therapy.	**5 patients:** Of 4 patients able to tolerate drug, 2 were asymptomatic, 1 had significant and 1 had minor or grade 4 improvement. Dose was reduced in 1 patient because of gastrointestinal distress. Drug was stopped in 1 patient because of itching of the skin.

**Of 6 patients classified as showing grade 4 improvement, 3 were unable to tolerate the drug and 3 showed unsatisfactory improvement under medication.*

***Of 8 patients classified as showing grade 4 improvement, 6 were unable to tolerate the drug, and 2 showed unsatisfactory improvement under medication.*

weakness with or without atrophy. An increase in sense of well-being occurred in one patient; however, depressed psychomotor activity usually remained unaltered. Increased sedimentation rates and serum polysaccharide-protein ratios were noted in all patients; they returned to normal in 8 of 26 patients receiving hydroxychloroquine sulfate, and in 4 of 25 patients receiving chloroquine phosphate. No patient had abnormal changes in the blood count.

Side effects (Table 3). Headache or blurring of vision, which disappeared spontaneously after a few weeks, occurred in five patients and gastrointestinal symptoms in four of the 26 patients receiving hydroxychloroquine sulfate; medication was stopped in two of the latter four patients because of the severity and persistence of symptoms. One patient developed a maculopapular rash with mild exfoliation over the hands and feet; the drug was stopped. Increased nervousness and lightheadedness associated with mild temporary mental confusion during the first week of therapy were noted in one patient. These symptoms subsided spontaneously during the second week of therapy.

About one half (13) of the 25 patients who received chloroquine phosphate noted headache or blurring of vision, symptoms that usually were transient and subsided spontaneously in from two to four weeks. Varying degrees of gastrointestinal distress (anorexia or nausea) were noted in eight patients. These symptoms were partially alleviated by medication taken with meals; occasionally they subsided spontaneously or by reduction in dosage, but in three patients they were so severe that administration of the chloroquine phosphate had to be stopped and hydroxychloroquine sulfate then was substituted. In two patients dermatitis developed within two weeks after chloroquine phosphate therapy was started and medication had to be discontinued. In one patient the maculopapular rash disappeared within 36 hours after medication was stopped, but in the other patient exfoliative dermatitis developed. Another patient noted generalized itching of the skin, which disappeared when administration of chloroquine phosphate was stopped. An increase in nervousness and aggravation of pre-existing insomnia occurred in one patient, and tinnitus and lightheadedness in another, but these symptoms subsided when the dose was reduced.

Contraindications

The antimalarial agents appear to cause very few serious side actions in rheumatoid arthritis and consequently there are few contraindications to their use in this disease. Because of high concentrations of the drugs found in the liver, it is our opinion that these drugs should not be used or, if used, used with caution in the presence of hepatic disease. They should not be administered again if a skin reaction occurs. Severe gastrointestinal symptoms, nervousness, or persistent tinnitus are other possible contraindications. Leukopenia did not occur in this study but it should be kept in mind and watched for during therapy.

Table 3. — *Side effects in patients having rheumatoid arthritis treated with hydroxychloroquine sulfate*

Table 3.—*Side effects in patients having rheumatoid arthritis treated with hydroxychloroquine sulfate or with chloroquine phosphate*

Side effect	Number of times noted in 26 patients receiving hydroxychloroquine sulfate	Hydroxychloroquine sulfate			Number of times noted in 25 patients receiving chloroquine phosphate	Chloroquine phosphate		
		Maintained	Reduced	Stopped		Maintained	Reduced	Stopped
Not clinically significant								
Blurring of vision (transient)	2	2	0	0	5	5	0	0
Headache (transient)	3	3	0	0	8	8	0	0
Lightheadedness (transient)	1	1	0	0	1	1	0	0
Mental confusion (transient)	1	1	0	0	0	—	—	—
Nervousness	1	0	1	0	2	0	2	0
Tinnitus	0	—	—	—	1	0	1	0
Clinically significant								
Anorexia *	2	0	1	1	4	0	2	2
Dermatitis	1	0	0	1 (Maculopapular with local exfoliation)	2	0	0	2 (1 maculopapular, 1 exfoliative)
Itching	0	—	—	—	1	0	0	1
Nausea *	2	0	1	1	4	0	3	1
Leukopenia	0	—	—	—	0	—	—	—

**These studies were carried out with uncoated tablets. Recently both drugs have been coated with approximately 2 mg. of pharmaceutical-grade shellac,[44] which has reduced appreciably the incidence of gastrointestinal side effects; however, further study will be necessary pertaining to intestinal absorption.*

Comment

Hydroxychloroquine sulfate, one of the new 4-aminoquinoline antimalarial agents, has a significant but limited anti-inflammatory effect on active rheumatoid arthritis. It has an advantage over chloroquine phosphate: it causes less gastrointestinal disturbance and can be administered in larger doses during the initial period of therapy, which appears to be necessary occasionally. However, we do not believe that hydroxychloroquine sulfate administered in comparable dosage results in greater anti-inflammatory response than that from chloroquine phosphate in the treatment of rheumatoid arthritis. In our series, 15 of 26 patients receiving hydroxychloroquine sulfate became asymptomatic, as compared to 9 of 25 patients receiving chloroquine phosphate. The therapeutic effect was limited with either drug, and patients with mild disease improved more quickly and more completely than those with severe, deep-seated disease.

Skin reactions occurred after using either drug, but it usually was possible to continue treatment after the lesions had disappeared, by substituting the other antimalarial agent for the drug that had precipitated the reaction.

The mechanism by which an antimalarial agent suppresses inflammation in rheumatoid arthritis has not yet been established. High concentrations of the drug have been found in the liver, spleen, lungs, and skin.[11] The high concentrations found in the skin are believed to be responsible for the effectiveness of the drug in the treatment of discoid lupus erythematosus. According to Haydu[45] the effectiveness of chloroquine phosphate in the treatment of rheumatoid arthritis is related to its influence on the activity of adenosinetriphosphate (ATP). He believes that the tissue requirements of ATP are increased in this disease and that chloroquine phosphate is effective because of its inhibition of adenosinetriphosphatase (ATPase) activity.

It is concluded from our study that hydroxychloroquine sulfate is moderately effective in suppressing inflammation of rheumatoid arthritis but has no apparent effect on psychomotor activity. It has a high degree of clinical safety and can be used in combination with other therapeutic agents in patients with severe disease. It is considered to be the preferred antimalarial drug for treatment of disorders of connective tissue, because of the low incidence of gastrointestinal distress as compared to that with chloroquine phosphate. The incidence of significant toxicity reactions occurring from the use of either antimalarial agent in the long-term treatment of rheumatoid arthritis has been less than was anticipated, and no instance of leukopenia has been observed in any of the patients of this study, and in well over 250 patients who are not included in this study but who are receiving one of these drugs at the present time. Recently both antimalarial drugs have been coated with pharmaceutical-grade shellac,[44] resulting in further decrease of gastrointestinal disturbance. Preliminary studies suggest that intestinal absorption with the coated tablets is comparable to that with the uncoated tablets.

V. CHEMOTHERAPY IN RHEUMATOID ARTHRITIS: A CONCEPT

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RHEUMATOID ARTHRITIS is a variable and unstable disease that disappears spontaneously or responds quickly to nonspecific measures in approximately half of the patients seeking medical care.[46] In the patients in whom the disease does not respond satisfactorily to simple measures, treatment becomes difficult, and in approximately one third of those patients the disease may become so intractable as to defy almost any method of therapy.

To be completely efficacious in the treatment of rheumatoid arthritis, a therapeutic agent must be nontoxic and able quickly to suppress the acute phase of the disease, to elevate mood or to counteract emotional instability when present, to prevent relapses, and constantly to suppress chronically active disease associated with persistent inflammatory joint manifestations, while permitting the maintenance of useful activity. Unfortunately, no single therapeutic agent, or, heretofore, any combination of agents has been capable of fulfilling all of these criteria. We believe that our present therapeutic program comes closer to the ideal than any therapy that we have used previously. Inasmuch as each of the drugs that have been used possesses a different pharmacologic action, it appeared logical that results could be improved and the danger of toxicity could be reduced by administering a combination of drugs each in a dose smaller than that which ordinarily would be used if the drug were employed alone. An exception was the antimalarial agents (hydroxychloroquine sulfate and chloroquine phosphate), the dosage of which was not reduced since they rarely cause toxic reactions.

Our program of therapy for patients with rheumatoid arthritis begins with an analgesic and becomes increasingly complex as the disease increases in severity. Unless the disease is obviously progressive or a simple drug program previously has been unsuccessful, simple methods of therapy are instituted before resorting to the combined-drug programs.

Physiotherapy, which is not discussed in detail here, is considered essential in patients with musculoskeletal symptoms. It was used routinely when indicated, supplementing each chemotherapeutic program.

Analgesic and Tranquilizing Agents

Patients with early or nonprogressive disease who were able to maintain light-to-moderate activity were initially given sodium salicylate, from 4 to 8 gm. daily. The salicylate was administered primarily for its analgesic effect, rather than for its anti-inflammatory effect which we consider insignificant in comparison to that of certain nonsteroid drugs now available. Subjective and objective responses to treatment were evaluated at from six- to eight-week intervals for from three to six months. When mild alteration in the patient's affect or in his emotional stability accompanied the arthritis, one of the tranquilizing and muscle-relaxing agents was given in addition to the salicylate. The most effective agent available at present is meprobamate*, administered orally in doses of 400 mg. three or four times daily. Recently phenaglycodol** has been used in doses of 200 mg. three times daily, but we have not completely evaluated its effect at this time. Depressed states may occur from overdosage. Usually these drugs can be discontinued as anxiety states subside and confidence is restored.

Anti-Inflammatory Agents

Hydroxychloroquine sulfate or chloroquine phosphate. The antimalarial drugs were administered to those patients who did not respond satisfactorily to salicylate, to those patients who had more active or deep-seated disease, to those patients who had associated diseases contraindicating the use of corticosteroids, such as diabetes mellitus, tuberculosis, peptic ulcer, and to certain patients with hypertension. The usual dosage of hydroxychloroquine sulfate ranged from 400 mg. to 600 mg. daily, although in some patients improvement was delayed for a matter of weeks or remained incomplete even when the daily dose was increased to 1.0 gm. The usual dosage of chloroquine phosphate initially was 500 mg. daily, which for most patients was decreased to 250 mg. daily after improvement had occurred. Gastrointestinal side effects often prevented the administration of a larger initial dose of chloroquine phosphate, but with hydroxychloroquine sulfate these effects were not so frequent.

Decrease in joint swelling with lessening of pain in joints and muscles usually was the first manifestation of improvement. Patients often stated that their joints "felt looser" before there was an apparent decrease in joint size. In patients with moderately severe rheumatoid arthritis the improvement frequently was incomplete, especially during the first three months and up to six months of treatment. In some cases salicylate, from 4 to 8 gm. daily, or prednisone, 3 mg. daily, also was administered, while in others more resistant to therapy a combination of drugs was utilized (page 107).

ACTH. When antimalarial therapy was supplemented by prednisone for more than a few weeks, ACTH gel, 10 units, was given intramuscularly at

**Equanil, Wyeth Laboratories; Miltown, Wallace Laboratories.*
***Ultran, Eli Lilly and Company.*

weekly intervals. We have observed repeatedly that patients receiving maintenance antimalarial therapy and from 3 to 6 mg. of prednisone or a related steroid, maintain more satisfactory improvement and have fewer fluctuations in disease activity if they also receive a small amount of ACTH. The dose is too small to produce hyperfunction of the adrenal cortex which will result in a measurable increase of plasma hydrocortisone, although it may cause minimal stimulation of the entire adrenal cortex and result in a mild subclinical state of hypercorticalism that is clinically desirable in patients with rheumatoid arthritis. No significant degree of anterior hypopituitarism is believed to result from the administration of this amount of ACTH. Wilson[47] has observed apparent steroid abnormalities in the urine of two male patients with rheumatoid arthritis as compared with that of normal males. He believed that the administration of ACTH diminished the abnormal steroid metabolites, which were replaced with the metabolite pattern found in the normal males. Holley[48] states that the diurnal steroid excretion pattern observed by Hill and Warren may not reflect variations in intermediary metabolism or in excretion of adrenocortical steroids, but a change in the "pituitary-adrenal or hypothalamic-pituitary-adrenal" secretory mechanism.

At present we consider the administration of ACTH in the dosage described to be an integral part of the chemotherapeutic program for patients with severe active disease that requires maintenance corticosteroid therapy.

Combined-Drug Therapy

For those patients incapacitated by persistently active disease, or for those in relapse who have been resistant to all previous treatment, a program of therapy has been devised in which certain drugs are administered in various combinations. The drug combinations and routes of administration vary depending upon the severity of the disease, the extent of inflammatory and destructive joint manifestations, the emotional state of the patient, and the previous therapy. For this treatment patients are hospitalized for two weeks during which time they receive chemotherapy, physical therapy, instruction in home physical therapy and in maintenance of chemotherapy, and proper shoes or orthopedic appliances if indicated.

Pharmacologic action varied for each drug, and it appeared that a greater therapeutic effect with fewer side reactions was achieved with multiple drugs than was achieved with larger doses of any single agent.

Induction therapy. We believe that the intravenous administration of ACTH and HN_2 in the doses recommended is one of the quickest and safest methods of suppressing generalized activity of rheumatoid arthritis. Ten units of aqueous ACTH was diluted in 500 ml. of 5 per cent dextrose in water, andt he solution was infused over a period of four hours. To prevent nausea and vomit-

ing, 50 mg. of promazine hydrochloride was given at the beginning of the ACTH infusion. One-half hour later, 2 or 3 mg. of HN_2 diluted in 2 ml. of saline solution was injected directly into the intravenous tubing. When the gastrointestinal side effects were properly controlled with promazine hydrochloride, most patients welcomed this therapy because of the rapid relief of symptoms.

Intravenous therapy was continued daily for five days and then stopped for from one to three days in order to evaluate the immediate results. If symptoms rapidly returned on the first day, four or five more daily infusions were given; if minor symptoms persisted or returned, two or three more daily infusions were administered. If no symptoms appeared after three days, no further infusions were given.

This treatment was most effective in suppressing soft-tissue swelling, fever, constitutional symptoms, and acute or subacute inflammatory joint swelling. Joint involvement manifested by thick pannus formation and persistent effusion did not subside completely. The suppressive effect was of short duration and symptoms usually reappeared in from four weeks to three months. However, the temporary remission usually was of sufficient duration to allow the oral maintenance therapy to become effective enough to maintain the suppression of disease activity without large doses of corticosteroids.

Oral maintenance therapy. An antimalarial drug, preferably hydroxychloroquine sulfate, was used for oral maintenance therapy, begun simultaneously with the ACTH and HN_2 intravenous therapy. The average initial total daily dose was 600 mg., one 200-mg. tablet after each meal. Prednisone or prednisolone, 1 or 2 mg. three times daily, also was given. This combination of orally administered drugs was continued until the patient was practically symptom free, usually for from 3 to 12 months, and then the dose of corticosteroid was reduced to half. If the disease remained suppressed after a few months, the corticosteroid was stopped, as it was assumed that the patient was experiencing a remission. Whether the remission was spontaneous or drug-induced is not known and is not important; rather, it is important to realize that alteration in the diseased state had occurred and permitted a modification of the drug schedule whereby the corticosteroid could be decreased in dosage or could be stopped. The remission sometimes persisted, but if an exacerbation occurred the corticosteroid again was added to the program of oral maintenance therapy. Exacerbations usually were infrequent after the first year of maintenance therapy in patients receiving one of the antimalarial drugs. Patients who were asymptomatic but in whom the disease remained active on the basis of laboratory studies were maintained on a reduced dose of an antimalarial, 250 mg. of chloroquine phosphate or 200 mg. of hydroxychloroquine sulfate. If all symptoms subsided and laboratory tests, including serum protein fractionation as determined by electrophoresis, erythrocyte sedimentation rate, and serum polysaccharide-protein ratio, returned to normal for three months the antimalarial drug was stopped.

ACTH administered intramuscularly. ACTH was used routinely in this program of therapy as described previously on page 106. The rationale for its use

has been discussed. The routine dosage was 10 units of long-acting ACTH injected intramuscularly once weekly. The patient or a close relative of his was instructed in the technic of administration. If during the first month or two of therapy the patient continued to have unstable disease associated with minor exacerbations, the dosage of ACTH was increased to 10 units twice weekly. Usually this increased dosage was necessary for only a few weeks, after which time the routine dosage was again administered. As improvement occurred and the corticosteroid was diminished in dose or stopped, ACTH was continued in the routine dosage for a few weeks after which time it was gradually reduced over a period of a few weeks and then it was stopped. When corticosteroid was restarted, ACTH, 10 units weekly, again was added to the therapeutic program.

Hydrazides. Isoniazid alone (in the dosage of 100 mg. three times daily) was inconsistently and incompletely effective in relieving joint manifestations. The action of iproniazid (in the dosage of 50 mg. three times daily for one month and then 25 mg. daily or every other day) was more consistent and relatively rapid, but the drug had to be used sparingly and adjusted to the response of the patient. Isoniazid and iproniazid were used alone or in combination with small doses of steroid, and as oral maintenance therapy in the program of combined-drug therapy before the antimalarial drugs were available. However, the hydrazides still are used when the antimalarial drugs are not tolerated or when there is a possibility of associated tuberculosis. Pyridoxine, from 10 to 25 mg. daily, was given with the hydrazides as prophylaxis against peripheral neuropathy. Withdrawal symptoms were not apparent when administration of the hydrazides was stopped.

Iproniazid we consider to be especially useful as a temporary adjunct to therapy in selected patients with various degrees of depression and emotional instability. Irrespective of the program of therapy decided upon for the patient, iproniazid can be administered in dosages of 50 mg. daily for from a few weeks to a few months, after which time the dosage gradually can be tapered to 25 mg. or less daily or every other day. After the patient has gained in weight and his strength and a sense of well-being have returned, administration of the drug can be stopped. Withdrawal effects were not apparent with this dosage schedule.

Intraarticular therapy. The program of combined chemotherapy discussed so far is effective mainly in suppressing constitutional symptoms, soft-tissue swelling, and acute or subacute inflammatory joint lesions. However, those joints that have been involved for years may have thick pannus formation and varying degrees of joint effusion which respond only partially to oral and parenteral therapy; often several of the larger joints may be resistant to treatment. Generally, an increase in the dosage of the medication being used will do little more than produce toxic reactions. Intraarticular injections of hydrocortisone or a related steroid may be of some value when this problem exists, but their effect is only temporary, usually lasting for from three days to three weeks. To prolong the effect of intraarticular therapy, small doses of HN_2 were mixed with a steroid in a ratio of 0.5 mg. of HN_2 (diluted in 0.5 ml. of normal saline

solution) to 25 mg. (1 ml.) of intraarticular steroid. This combination proved to be safe and effective, and in addition resulted in prolonged suppression of inflammation in wrist, knee, ankle, proximal interphalangeal, metacarpophalangeal, and elbow joints, which in many instances had been suppressed for only a few days or weeks.

When there were severe chondromalacia of the patella, advanced destruction of cartilage between the tibia and femoral condyles, severe pain on motion, and absence of fluid formation within the joint, the injections consisted of only hydrocortisone tertiary-butylacetate (H.T.B.A.) or a related steroid.

In more than 2000 intraarticular injections in which HN_2 was combined with H.T.B.A. or a related steroid, there has been no case of tissue sloughing or scarring. From our experience during the past three years, we believe that most joints (as described in part II) where persistent synovitis exists, but the disease is still potentially reversible, should be injected routinely at the onset of the combined chemotherapeutic program. These joints should be injected three times at from three- to four-day intervals. After one month, two or three additional injections at weekly intervals may be given. The results after two or three years have shown no complications from the use of HN_2, but 10- and 20-year follow-up studies are necessary to evaluate fully the cellular alteration that is produced by HN_2.

Chronic hypercortisonism. Slocumb [49-51] has described a syndrome termed *hypercortisonism* which results from prolonged hormonal overdosage and is characterized by emotional instability, fatigability, muscle and joint aches, and diffuse mesenchymal reactions that tend to simulate systemic lupus erythematosus and periarteritis nodosa. According to Slocumb, the problem of relieving hypercortisonism is more complicated than merely the stopping of hormonal therapy, since this may result in exchanging the undesirable effects of exogenous chronic hypercortisonism for the equally distressing effects of endogenous hypocorticalism (decrease of more than one and possibly all of the adrenocortical steroids) and its diffuse mesenchymal reaction. He states that treatment of hypercortisonism at best is slow, difficult, and perhaps inadequate because of the limited knowledge regarding the underlying biochemical and other mechanisms. The recommended treatment necessitates the patient's co-operation and involves extra rest and gradual reductions in the dosage of corticosteroids; it may have to be continued for longer than several months.

During the past two years 15 patients having hypercortisonism who were referred to us have been treated with slightly modified combinations of the drugs that we are using for severely active rheumatoid arthritis. In each instance the dosage of prednisone or prednisolone was reduced abruptly to 2.5 mg. three times daily. Iproniazid was administered in dosages of 50 to 100 mg. daily, depending upon the degree of psychomotor depression. (Usually the daily dose of iproniazid was 100 mg. for 7 to 10 days, 75 mg. for one week, and then 50 mg., after which time it was further reduced and regulated according to the improvement in the patient's affect and the activity of the deep reflexes as described on page 96.) Simultaneously, ACTH, 10 units in 500 ml. 5 per cent dextrose in

water, and HN_2, 2 to 3 mg., was infused over a period of four or five hours daily for seven days, as described on page 75. Usually symptoms began to subside on the first or second day of therapy. On the eighth day intravenous therapy was omitted and the patients were closely observed for return of symptoms. If mild symptoms returned, two or three more daily intravenous injections of ACTH and HN_2 were administered. If moderate symptoms returned, from three to five more daily intravenous injections were given. The total dose of HN_2 never exceeded 25 mg. during one course of therapy. Hydroxychloroquine sulfate, from 600 to 800 mg., was started at the time that prednisone or prednisolone was reduced in dosage to 7.5 mg. daily. Subjective improvement usually began on the third or fourth day: fatigability and weakness diminished and strength increased. After the intravenous therapy was completed, 10 units of repository ACTH was given three times weekly for three weeks after which time it was reduced gradually and maintained at 10 units weekly.

Patients usually were hospitalized for from two to four weeks, during which time facial rounding and fat pads in the supraclavicular and cervical regions began to subside significantly. Patients treated two years ago in this manner have remained improved and show no indications of chronic hormonal overdosage.

Our clinical results support the theory that these patients have exogenous hypercortisonism that subsides as the corticosteroid is rapidly decreased in dosage, and endogenous hypocorticalism that within 24 to 48 hours responds to intravenously administered ACTH and HN_2. However, this theory does not explain why the intravenous administration of HN_2 and ACTH also suppresses the hypercortisonism that results from excessive intramuscular administration of ACTH and that is characterized by endogenous hypercorticalism and endogenous anterior hypopituitarism. A possible explanation is that HN_2 through an unknown mechanism of action alters the response of the connective tissue to ACTH and corticosteroids so that these tissues again become sensitive to the suppressive action of the hormones.

Treatment of patients with hypercortisonism will be reported in more detail elsewhere. In brief, most patients have improved significantly and they are being maintained on a combined-drug program that eliminates the need for large doses of ACTH or of a corticosteroid.

Comment

The results of our program of combined-drug therapy for rheumatoid arthritis have been encouraging in most of our patients. One of the most important features of the combined therapeutic program has been the low incidence of toxic reactions related to hormone therapy. Sensitivity reactions to ACTH occurred in only 5 of the 254 patients. In 12 patients active duodenal ulcer was present at the time that treatment was started, and in two patients active duodenal ulcer developed after therapy had been started. These patients were treated with a conservative ulcer program while therapy for rheumatoid arthritis was continued. No instance of psychosis developed during therapy, and aggravation of hypertension and of diabetes was not clinically significant in this

series of patients. Our program is flexible and is adjusted on the basis of the activity of the disease in the individual patient. The theoretic effect of each drug of the entire therapeutic program on disease activity is depicted in Figure 1.

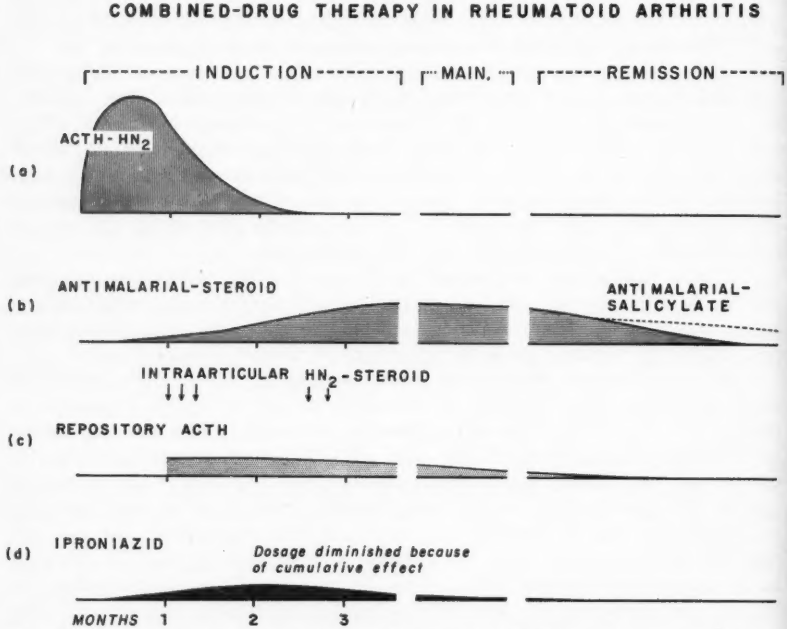

Fig. 1. Scheme of combined-drug therapy: Treatment is flexible and for convenience is divided into three phases. The induction phase includes (a) intravenously administered ACTH-HN_2: *ACTH*, 10 units, and *HN_2* from 2 to 3 mg., daily in 500 ml. of 5 per cent dextrose and water for 5 to 10 days. During this time maintenance therapy(b) is started, which does not become effective immediately: *Hydroxychloroquine sulfate*, from 400 to 600 mg. daily, or *chloroquine phosphate*, from 250 to 500 mg. daily, is administered with *prednisone* or *prednisolone*, from 3 to 7.5 mg. daily. (c) *Repository ACTH*, 10 units, intramuscularly administered weekly is started after induction therapy has been completed; the dosage may vary slightly during the first few months of treatment. The limitations of ACTH and corticosteroids are realized, despite their great effectiveness in suppressing disease activity; they are used intermittently in small doses, primarily as supplemental agents. (d) *Iproniazid*, from 50 to 100 mg. per day, is administered for from three to six weeks and then is reduced gradually.

Intraarticular injections are given when persistent but reversible joint inflammation is present.

The second or maintenance phase of therapy depicts the full effect of combined administration of *antimalarial-corticosteroid agents*, *repository ACTH*, 10 units administered at 7 to 10 day intervals, and *iproniazid*, finally reduced to 10 mg. daily or on alternate days as mood improves.

The third or remission phase depicts reduction in corticosteroids and antimalarial agents. *ACTH* is gradually reduced in dosage and administration is stopped when administration of the corticosteroid has been stopped. (b) *Salicylate* is substituted for corticosteroid as improvement occurs; it may be used as needed for minor aching and stiffness. If relapse occurs the drugs can again be administered as described.

Two hundred fifty-four patients who received combined-drug therapy, including one of the antimalarial agents as oral maintenance therapy, were followed for two years. Joint improvement, as determined objectively, was considered to be excellent or good in 223 of the 254 patients. One hundred sixty-one of these 223 patients received supplemental intraarticular injections of HN_2 and a steroid to obtain this degree of improvement. Emotional instability and depressed psychomotor activity observed in 187 of the patients were improved significantly in 125 patients.

We believe that our results were influenced by the patient's co-operation and motivation, and that these in turn were improved by the medication administered for that purpose while other medication was being used to suppress the objective disease manifestations.

Summary and Conclusions

1. Rheumatoid arthritis is a complex, fluctuating, systemic disease of unknown etiology, for which no single therapeutic agent to date is consistently or predictably effective.

2. A flexible program of chemotherapy is being utilized, from the oral administration of sodium salicylate alone, to the oral, intravenous, intramuscular, and intraarticular administration of multiple drugs (HN_2, corticosteroids, antimalarials, iproniazid).

3. With a variable therapeutic program, in our experience, it usually has been possible to achieve rapid suppression of acute disease, and to maintain suppression of chronically active disease through long-term therapy; fluctuating disease has become more stable and affect has been improved.

4. The incidence of toxic reactions and side effects has been minimal in relation to the number of drugs used.

5. The combined-drug regimen has given many additional months of gainful employment to certain patients who had responded unsatisfactorily to single therapeutic agents and who heretofore had been unemployable during periods of disease activity.

6. A program of therapy similar to that for severe, active, rheumatoid arthritis is suggested as being applicable to hypercortisonism.

7. Contraindications to the use of combined-drug therapy are few, notably hepatic disease and bone marrow depression.

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GASTRIC SURGERY IN ELDERLY PATIENTS

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ELDERLY patients are correctly regarded as substandard risks for abdominal operations. Possibly because of this fact and the additional precautions that surgeons habitually exercise for the elderly, it is noteworthy that indicated operations for gastric or duodenal lesions can be performed just about as safely in the elderly patients as in the young ones. There are two exceptions to the over-all safety existing for elderly patients: generally, there is a sharp increase in the incidence of nonfatal complications involving the cardiovascular system, urinary tract, and lungs after age 60 years; and similarly, there is a greater likelihood of postoperative mortality in the hospital, or within one month, for elderly patients suffering from malignant gastric lesions that are surgically incurable, than for younger patients with a similar condition.

In analyzing the results of gastric surgery one should differentiate the conditions for which the operations were performed. A convenient grouping separates those patients having operations for malignant disease from those having surgery for benign conditions. For example, some selection is possible in operations for duodenal ulcer; on the other hand, transabdominal exploration is performed in all patients with malignant disease unless there is irrefutable evidence that there is metastatic spread beyond the possibility of cure. Rarely, in malignant disease, has surgical intervention been inadvisable because of the poor condition of the patient. This circumstance, occurring in less than 5 per cent of my personal series, is illustrated by two cases.

Case 1. No operation for hopelessly advanced cancer. A 75-year-old retired farmer had been well until about nine months previously when he had an episode of hematemesis. Subsequently he had bled on several occasions. He had been jaundiced for a week, and was so severely prostrated that he was unable to get out of bed. The patient had lost 46 pounds in weight. Examination disclosed a weak, icteric, elderly man with an enlarged liver and a vague epigastric mass. Roentgenograms showed apparent involvement of the distal three-fourths of the stomach by an infiltrating neoplasm, including a widening of the duodenal loop. It was believed that this patient would not survive an exploration and that there was overwhelming presumptive evidence of incurability of the lesion. No operation was performed. He was discharged home and died two weeks later.

Case 2. No operation for cancer giving minimal symptoms and in a very unfavorable location. A 76-year-old retired man had mild digestive symptoms from "gas" for several months before examination. Roentgenograms showed evidence of a malignant neoplasm at the cardiac end of the stomach. Probable metastic nodules were palpated during the digital rectal examination; they were inaccessible to needle biopsy. Since the

patient had minimal symptoms and since the risk is great and the outlook poor in all operations for lesions of the cardia, three consultants were in agreement that operation was inadvisable. The patient continued his quiet life at home, did not develop obstruction, and had a gradual, painless decline; he lived approximately six months.

Malignant Disease

The mortality from the operations for gastric malignancy always will be substantially higher than that for benign gastric conditions, because the preoperative status of the patient often is poor and difficult to improve, and because the surgeon makes every effort to remove even a very extensive lesion if a cure seems possible. Figure 1 indicates the age distribution and mortality in a personal series of 114 consecutive patients who underwent resection for apparently curable gastric malignancy; the mortality is gratifiyingly low even for patients

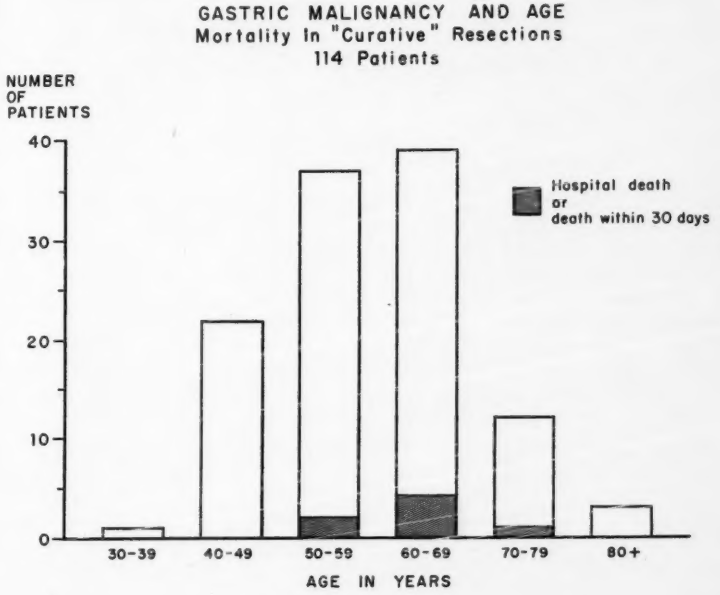

Fig. 1.

more than 70 years of age. By way of contrast, Figure 2 illustrates the mortality for 105 consecutive patients in whom the lesion was surgically incurable; here the risk is seen to increase sharply after the age of 60 years. Nevertheless, justification for operating on these elderly patients is to be found in the fact that some will have curable lesions, as in the following case.

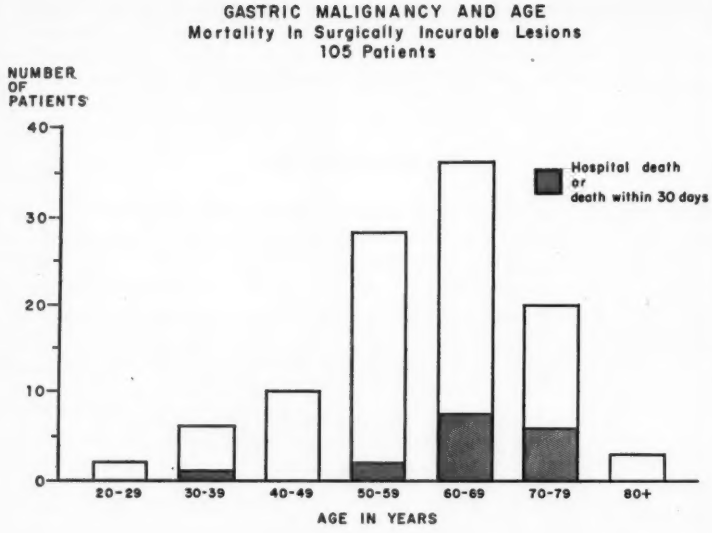

Fig. 2.

Case 3. Good result in conservative resection for large obstructing cancer. A 79-year-old retired business man, previously well, developed vague epigastric distress, then vomiting, within a period of 10 days. The patient seemed to be a vigorous man. Roentgenograms showed a large neoplasm at the lower end of the stomach. There was no evidence of distant metastatic spread. At operation a large fungating necrotic polypoid tumor, filling the entire antrum of the stomach and extending along the lesser curvature well into the pars media, was conservatively resected; approximately half of the stomach was preserved. No effort was made to perform a radical operation, although an extension of the cancer into the transverse mesocolon was resected en bloc with the stomach, and all tumor tissue was apparently removed.

The pathologic report was carcinoma of the stomach (massive), body and pylorus, with the proximal line of resection widely free and the distal line within 1 mm. of the neoplasm. No involved lymph nodes were apparent. The patient had an entirely uneventful postoperative course and was discharged on the eighth day. He has been seen periodically since and is vigorous and healthy five years from the time of operation. The patient now is 84 years old and his weight has been maintained at the preoperative level of 165 pounds.

Benign Disease

In a personal series of 410 consecutive operations performed for benign disease of the stomach and duodenum—including gastric ulcer, duodenal ulcer, jejunal ulcer, and miscellaneous conditions such as polyps, gastritis, negative

exploration for cancer, but excluding acute perforations—there were three deaths (Fig. 3). It is apparent that this type of surgery can be considered relatively safe in all age groups taken as a whole.

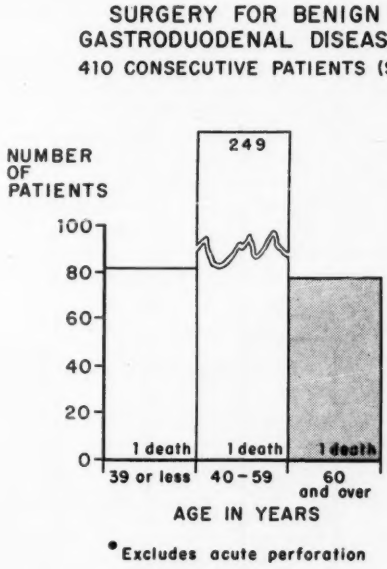

Fig. 3.

Gastric ulcer. In a series of 140 consecutive patients who had gastric resection for benign gastric ulcer and its various complications (excluding acute perforation), there was one death, that of a man aged 66 years (Case 4). The late results were good both in old and in young patients. In the group of patients more than 60 years of age, however, the incidence of nonfatal cardiovascular, pulmonary, or urinary tract complications, was 18 per cent; whereas it was 0 per cent in the group younger than 40 years of age, and only 6 per cent in the group between 40 and 59 years of age. The one fatality occurred as follows.

Case 4. Death from suppurative pancreatitis after gastrectomy for benign ulcer. A 66-year-old man had diabetes with advanced Laennec's cirrhosis, moderate hypertension, and arteriosclerotic cardiac disease. He had a subtotal gastric resection and a cholecystectomy for a large gastric ulcer and gallstones. The ulcer had penetrated into the pancreas. The patient did poorly following operation and, despite every supportive effort, died 11 days later. At autopsy there were an acute suppurative and necrotizing pancreatitis, a purulent peritonitis, and a severe cirrhosis of the liver of the Laennec type.

Duodenal ulcer. Although a majority of the 220 patients operated upon for duodenal ulcer (excluding acute perforation) could not be classed as elderly,

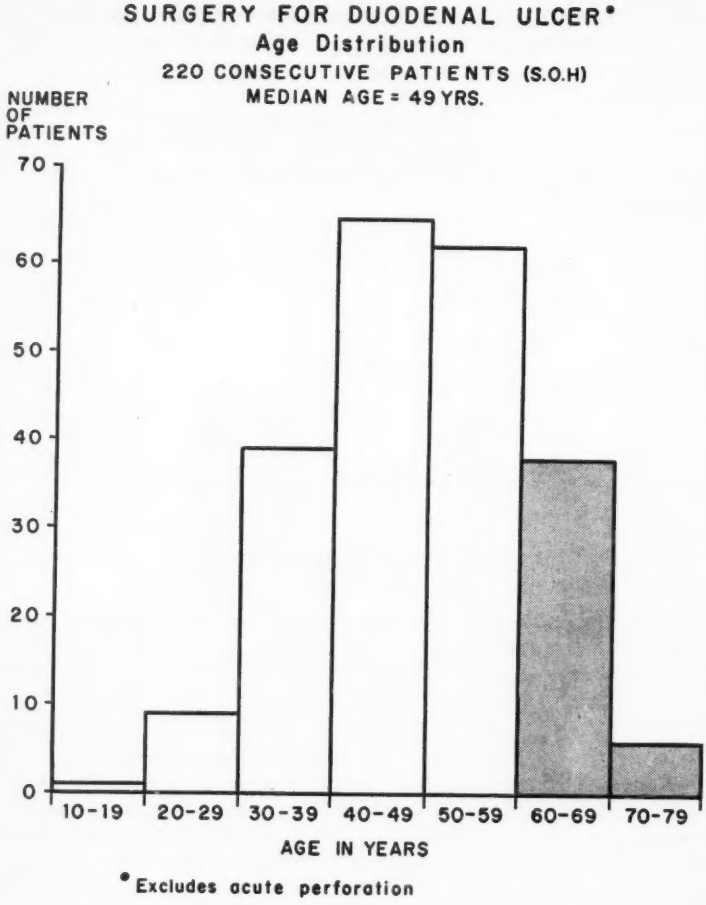

Fig. 4.

a fair number were not young (Fig. 4). It is obvious that in this group of patients a more careful selection for operation is possible than in the group of patients in whom a gastric malignancy is suspected. If the disease can be controlled on a medical regimen, operation will not be performed. However, elderly patients, like younger ones, bleed, are subject to obstruction, and they also may suffer from uncontrollable pain; such complications may make operation mandatory. The two deaths in this series of 220 patients with duodenal ulcer occurred in men under the age of 50 years; but again, it is to be noted that the incidence of

nonfatal complications involving cardiovascular system, urinary tract, and lungs, was 32 per cent in patients 60 years of age or older, as contrasted with 4 per cent in patients who were younger than 40 years of age. The safer vagotomy and gastroenterostomy as opposed to any type of resection would seem to be particularly applicable in this older age group as in the following case.

Case 5. Vagotomy and gastroenterostomy for obstruction and hemorrhage from duodenal ulcer. A 76-year-old farmer with a duodenal ulcer had been followed for four years. He was hospitalized once for obstruction, and once after hematemesis, and required four pints of blood. Although operation was advised on several occasions, he refused it. Finally, because of persistent pain, he consented to operation, and a subdiaphragmatic vagotomy and posterior gastroenterostomy with feeding jejunostomy was performed. His convalescence was uneventful and he was discharged on the eighth postoperative day. He has remained symptom free and when last heard from, four and one-half years after operation, he described himself as entirely well and very happy at the age of 80 years, hoping he would be able to answer our annual inquiry for the next 25 years!

Discussion

On the basis of the foregoing results it would seem that elderly patients can undergo necessary gastric operation with not much greater risk to life than younger persons, although the danger of nonfatal cardiovascular, pulmonary, or urinary tract complications increases with advancing age.

Certain principles should be adhered to with great strictness before one undertakes "elective" surgery in elderly patients. First, the surgeon should be even more certain than usual that measures short of surgery will not manage the disease successfully. Secondly, he also should be certain that the patient himself actively desires the operation. All experienced surgeons have the impression that the patient's attitude is of particular importance, if not a decisive factor, in the way he combats a serious postoperative complication: a patient's fighting spirit may provide the margin of safety, and a lack of interest in life may result in death. Finally, the surgeon should be willing to take plenty of time in getting the patient into optimal condition before operation. This will include not only correction of anemia, protein deficiency, or electrolyte imbalance that exist beforehand, but the postponement of the operation if there is a history of recent upper respiratory infection. The use of depressant drugs should be kept to a minimum both in the preoperative and in the postoperative phase, and only small doses of narcotics should be employed. It is especially important to have skillful management of anesthetics. Although nearly all of the elderly patients reported here had general anesthesia with endotracheal intubation and the use of muscle relaxants, the anesthesiologists made special effort to have the patients responsive and moving shortly after the conclusion of the operation. I am certain that avoidance of many of the possible complications in the early postoperative course are a direct result of the skillful management of anesthesia by the anesthesiologist, which not only makes the operation easier for the surgeon but also

immeasurably safer for the patient. In elderly patients the use of a tube gastrostomy from the stomach or its remnant will avoid the need of a Levin tube; it is our clinical impression that not only is the patient more comfortable, but that danger of chest complications is thereby decreased.

In the postoperative course the patient must be ambulated frequently. Postoperative ambulation is not to be confused with the ill-advised hoisting into the vertical position of an exhausted, debilitated, elderly patient merely to satisfy a surgical principle. *Ambulation* means *walking* and patients should stretch their legs themselves. Sitting in a chair probably is undesirable unless the legs are elevated. The patient should not sit on the edge of the bed and dangle the legs; the feet should rest on a chair and there should be no pressure on the back of the thighs or calves—to allow a patient to do otherwise is to invite venous thrombosis. Finally, elderly patients have had a long time to develop habits and whims; it is in the interests of all concerned to indulge them in every possible way. It may be that the elderly patient would like the family to bring him specially prepared broccoli, or that he wishes to chew tobacco, or that he has a minor superstition that he wants to have humored. The bedside attendants should allow the elderly patient as much latitude as is consistent with his safety in satisfying these personal desires.

Summary

Elderly patients withstand necessary gastric operation about as well as younger patients, from the standpoint of mortality, although the incidence of nonfatal complications involving the cardiovascular system, urinary tract, or lungs is markedly increased. With a careful selection of patients for operation, skillful management of anesthesia, and preoperative and postoperative care aimed at securing the optimal physical condition with a minimal use of depressant drugs, gastric operations on elderly patients can be performed with reasonable safety.

ANGIOGRAPHY OF THE CORONARY ARTERIES IN DOGS

III. During Perfusion With a Heart-Lung Machine in Combination with Cardiac Arrest in Coronary Artery Surgery

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TWO previous articles have reported our experience with angiography of the coronary arteries in living dogs: the first[1] described the technic in dogs with normal coronary arteries and the second[2] showed that surgically produced defects in the coronary arteries could be recognized. This paper describes an extension of the work. Angiography was performed on the animals on the operating table while the circulation was being maintained by a pump-oxygenator and reparative work on the coronary arteries was done. There were three specific aims: (1) to obtain satisfactory diagnostic angiograms of the coronary arteries at the time of operation (which will be mandatory before surgical repair of the coronary arteries of patients can be attempted); (2) to find a contrast medium that might safely be mixed with potassium salts used to produce elective cardiac arrest; and (3) to evaluate roentgenographically the anastomotic or reparative procedure before the chest was closed.

Material and Method

Ten mongrel dogs were used, weighing from 15 to 25 kg. The animals were given morphine sulfate as a preanesthetic and were anesthetized with either thiopental sodium (Pentothal sodium, Abbott) or pentobarbital sodium (Nembutal sodium, Abbott). Procaine hydrochloride (Novocain, Winthrop) was used locally for skin anesthesia and for intercostal block. The heart-lung machine was connected in the usual manner.[3] The blood was drawn into the machine from the venae cavae through cannulae inserted through the jugular

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**Formerly Special Fellow in the Division of Research.*

and femoral veins and returned through cannulae in both femoral arteries. A roentgen tube was mounted over the table at a target distance of 48 inches.

The animals were placed in the right posterior oblique position and a thoracotomy through the left fourth interspace was performed. Occasionally the fourth rib was removed. Tapes were placed to encircle the two venae cavae and the ascending aorta. A cardiac catheter was passed into the root of the aorta by way of the subclavian artery or one of its branches. After the artificial heart-lung had been started and the venae cavae and the ascending aorta had been occluded by tightening the tapes, 20 ml. of a solution composed of 10 ml. of 90 per cent Hypaque sodium (sodium diacetrizoate, Winthrop), 3 ml. of 25 per cent potassium citrate,[4] and 7 ml. of 0.95 per cent saline solution, was rapidly injected through the catheter. During the last second of the injection before the heart had completely stopped, the first roentgenogram was made using an exposure of 1/10 second at 70 kilovolts (Fig. 1).

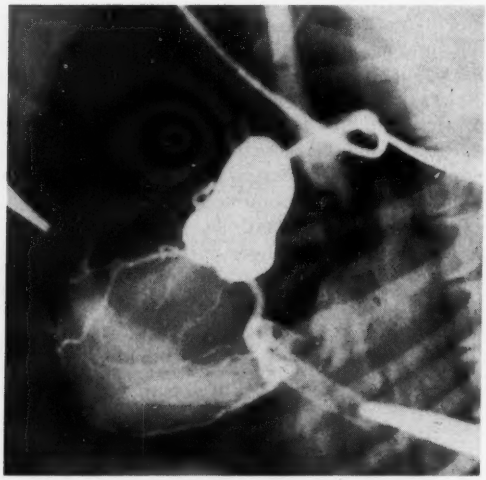

Fig. 1. Angiogram taken at the moment of cardiac arrest with the venae cavae and the aorta occluded with tapes. The cardiac catheter with its tip at the aortic base has been introduced through a branch of the left subclavian artery. All three coronary arteries are well filled.

An operation on the coronary arteries was completed during the period of arrest while the aorta and the subclavian artery remain occluded. An anastomosis between the subclavian artery and a major coronary artery was made either directly or by means of an interposed freeze-dried arterial graft. The cardiac catheter previously used for injection of the contrast Hypaque-potassium mixture was employed as a splint for the suturing. When the anastomosis had been completed the aortic tape and a bulldog clamp occluding the subclavian artery simultaneously were removed so that the coronary arteries were perfused. Usually the heart started to fibrillate. This fibrillation was allowed to continue

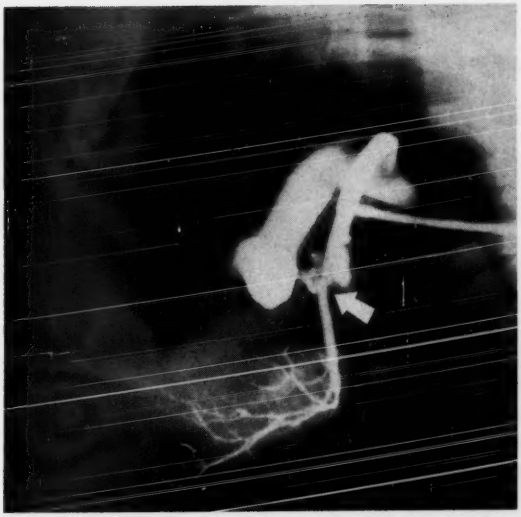

Fig. 2. Angiogram taken after completion of an end-to-end anastomosis between the left internal mammary artery and the left circumflex artery. (The left subclavian artery has been divided distally to the internal mammary and turned downward.) Backflow of the contrast medium fills the aortic arch and base. A small leak at the anastomosis is evident. This leak disappeared when the heparin was neutralized.

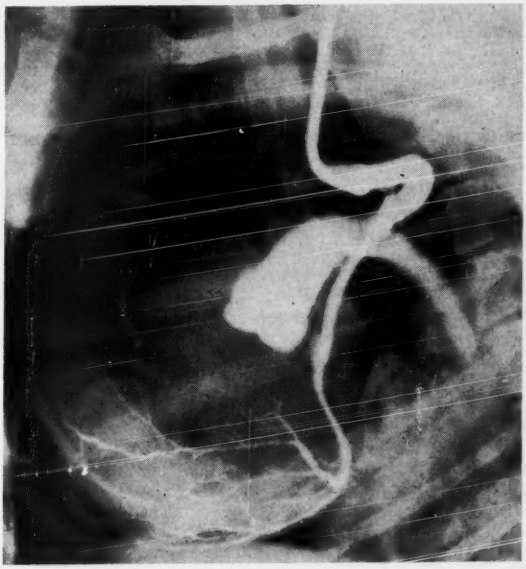

Fig. 3. Angiogram taken after completion of an end-to-end anastomosis between the left subclavian artery and the left circumflex artery, employing an interposed freeze-dried graft.

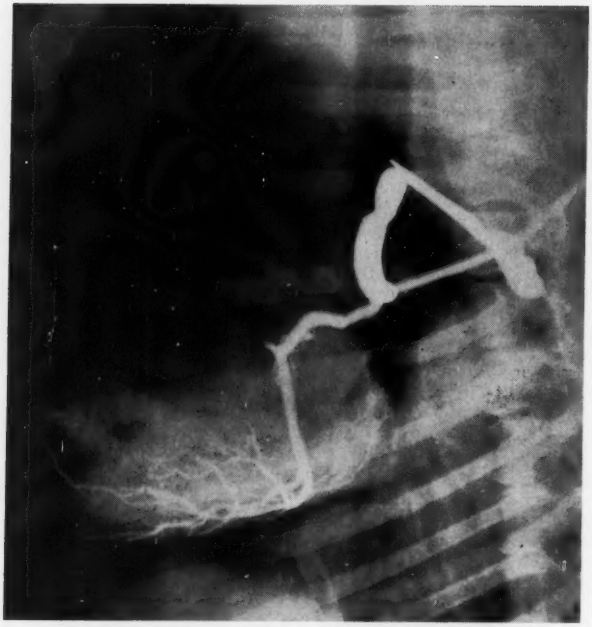

Fig. 4. Angiogram showing same type of anastomosis as that shown in Figure 3. Here the subclavian artery is occluded with a clamp so that no backflow into the aorta is seen.

for 10 minutes, during which time a second arteriogram was made to evaluate the anastomosis. Four to 8 ml. of 90 per cent Hypaque sodium was injected through the cardiac catheter into the subclavian artery and another roentgenogram was made just before the end of the injection. The root of the subclavian artery sometimes was clamped to obtain a more intense image of the anastomosed vessels, otherwise a retrograde flow also would outline the base of the aorta (Figs. 2, 3 and 4) and occasionally the untouched coronary arteries.

After the roentgenogram had been made, the heart was defibrillated using one electric shock or a series of shocks as necessary.* As soon as the dog could support its own circulation, the heart-lung machine was disconnected. If the machine could not be safely disconnected one hour after the defibrillation, the dog was sacrificed and the anastomosis was examined. The surviving dogs were carefully observed and serial electrocardiograms were made.

Results

Satisfactory diagnostic angiograms were obtained in all 10 dogs. After the

*Defibrillator giving a shock of 1 second at 110 volts was made by Frederick Olmsted, Division of Research.

completion of the anastomoses and the simultaneous release of the occlusions of the aorta and of the subclavian artery, ventricular fibrillation occurred in nine dogs; but in each, electroshock arrested the fibrillation and effective heart beats followed. In one dog a normal sinus rhythm was obtained immediately without electroshock and the second injection of contrast medium did not affect the sinus rhythm.

Whether the dogs survived or not seemed to depend on the blood flow through the anastomosis. The duration of cardiac arrest ranged from 36 minutes to 3 hours and 58 minutes; the average time was 82 minutes. In all 10 dogs an effective beat was restored despite cardiac arrest for a period greater than one hour.

Five dogs failed to maintain an adequate blood pressure and were sacrificed. In four dogs this failure resulted from narrowing at the point of anastomosis. In one dog a low rate of perfusion was the most likely cause of myocardial insufficiency. Five dogs survived* and have shown no sign of myocardial damage due to the contrast Hypaque-potassium mixture.

Summary

A technic for coronary angiography in dogs during perfusion with a heart-lung machine is described. An injection of potassium citrate with 90 per cent Hypaque sodium made it possible simultaneously to arrest the heart and to obtain a coronary angiogram. The contrast medium in combination with potassium citrate caused no apparent damage to the myocardium even when the mixture remained in the heart during periods of arrest exceeding one hour. The technic allows films of diagnostic quality to be taken on the operating table at the moment of cardiac arrest, and also after an anastomosis has been performed, in order to evaluate the immediately postoperative anatomic result.

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Addendum

After completion of this study, two papers reporting successful angiography of the coronary arteries in a man came to our attention: Di Guglielmo, L., and Guttadauro, M.: Sulla visualizzazione radiologica delle arterie coronarie nel vivente; rassegna di 413 osservazioni. La Radiologia Medica, Anno XL Fasc. 10, Oct. 1954; and Di Guglielmo, L., and Guttadauro, M.: Anatomic variations in coronary arteries; arteriographic study in living subjects. Acta radiol **41**: *393-416, May 1954.*

**The late results of these grafts have been unsatisfactory: thrombosis occurred at the junction of the subclavian artery with the freeze-dried graft. In one recent experiment, heparinization, for one week following the operation, prevented thrombosis of the suture line.*

A DEMONSTRATION OF THE ROLE OF POTASSIUM AND CITRATE IONS UNDER THE CONDITIONS OF ELECTIVE CARDIAC ARREST FOR OPEN-HEART OPERATION

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SINCE the preliminary report[1] in April 1956, 75 more patients have undergone open-heart operations with elective cardiac arrest according to the Melrose technic[2] at the Cleveland Clinic Hospital. Cardiac arrest with potassium citrate permits the surgeon to operate in a quiet, relatively bloodless, open heart.

In this paper no new facts are presented, rather an attempt is made to demonstrate old and well-known truths concerning the effects of certain cations on the myocardium under the conditions of their present clinical application.

Ringer[3] was the first to study the effect of electrolytes on the heart muscle; Hering[4] arrested ventricular fibrillation in the perfused rabbit's heart with potassium and saw that the normal beat gradually redeveloped as soon as the perfusate had washed out the excess potassium. Wiggers[5] used potassium arrest as a standard laboratory experiment or demonstration for more than 40 years; undoubtedly others have similarly used it for many years. In 1927, concern about the increased death rate from accidental electrocution prompted simultaneous but independent investigations by Hooker[6] and by Wiggers.[7] They stopped ventricular fibrillation in intact animals by an electric shock or by intracardiac or intra-arterial infusion of potassium chloride. Calcium chloride was thereafter injected to re-establish the heart beat. Those studies formed the basis for cardiac resuscitation as it is now generally accepted. Montgomery, Prevedel, and Swan[8] used potassium chloride to stop ventricular fibrillation in hypothermia.

The conversion of ventricular fibrillation by injection of potassium salts is justified by the desperation of the situation. However, the premeditated arrest of the normally beating human heart was not practiced until it was suggested for clinical use in open-heart surgery by Melrose, Dreyer, Bentall, and Baker.[2]

This work was supported by a grant from the Cleveland Area Heart Society to Doctor Kolff.
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Melrose and associates perfused excised hearts with oxygenated Locke's solution by the method of aortic cannulation. Potassium citrate was added to the perfusate; 5 mg. per milliliter always caused complete cardiac arrest. Diastolic cardiac arrest always occurred within 20 seconds after infusion of the potassium solutions. During the period of arrest, coronary flow was stopped for 15 minutes without subsequent evidence of cardiac damage. Spontaneous beating usually resumed within three minutes after perfusion with pure Locke's solution. The heart rate was normal within less than one minute, and the force was almost fully recovered within an additional three minutes. Restarting of the arrested heart did not require stimulation but only perfusion of the coronary arteries with oxygenated fluid. Melrose and associates applied this principle in intact animals, establishing a technic that we have followed and described in detail.[9]

For the demonstration discussed in this report we used three dogs, each weighing approximately 10 kg. The dog's circulation was maintained with a heart-lung machine in the usual manner. Blood was withdrawn from both venae cavae, was oxygenated in an artificial lung and was pumped back into the aorta either through the subclavian artery or through one of the carotid arteries. The perfusion rate was at least 60 and sometimes 100 ml. per kilogram per minute, and during most of the experiments the blood pressure could be maintained at 50 at the least, and often at 80 or 100 mm. Hg, even when the dog's own heart was excluded from the circulation. A cardiac catheter was inserted through one of the carotid arteries into the root of the aorta. After occlusion of the venae cavae and clamping of the root of the aorta, equivalent amounts of electrolyte solutions were injected through the cardiac catheter into the root of the aorta. To compare the action of individual ions, solutions of 4.5 mEq. of the following salts were prepared, each in 20 ml. of water*: potassium chloride, potassium citrate, sodium lactate, and sodium citrate.

An electrocardiograph (lead 2) continuously registered the changes in the cardiac rhythm, which were verified by direct observations of the ventricles and auricles through the open chest during the experiments. After the effect of an electrolyte had been obtained, the clamp was removed from the root of the aorta; blood from the heart-lung machine then entered the coronary arteries and flushed the electrolyte out of the myocardium.

Potassium citrate, 4.5 mEq., was injected six times in the three animals either to defibrillate the heart or, toward the end of the experiment, to prove that the heart still could be stopped and started. Potassium citrate stopped the heart whether a sinus mechanism or fibrillation existed before the injection. Normal sinus rhythm was restored after release of the clamp from the aorta; fibrillation recurred once, necessitating a second injection.

Sodium citrate, 4.5 mEq., was used to test the effect of the citrate ion. In the first experiment (Fig. 1, *1B*), the cardiac rate decreased, the T waves

**Melrose diluted the potassium citrate in 20 ml. of blood, but for simplicity our solutions were diluted in 20 ml. of water.*

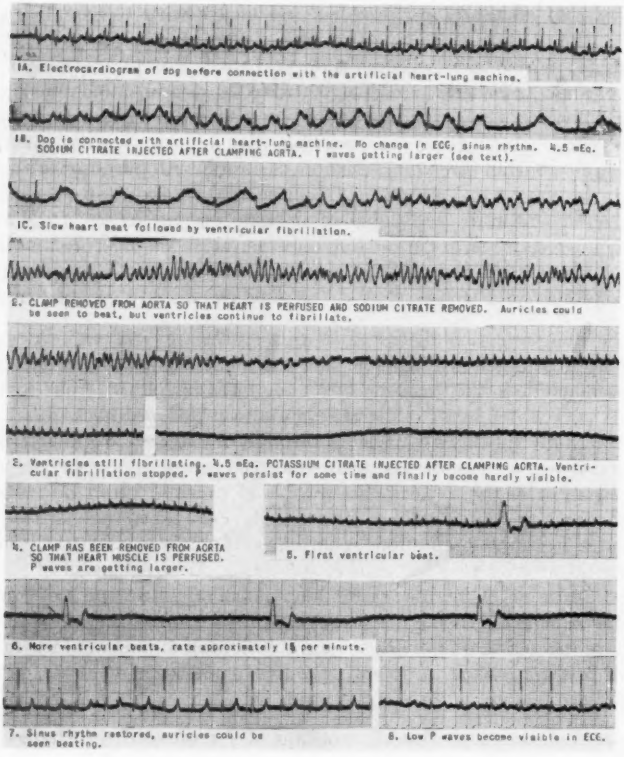

Fig. 1.

increased in voltage and duration, and the Q-T interval became prolonged. The latter change was so great that a 2:1 atrioventricular block occurred; it resulted from the fact that alternate P waves occurred before repolarization of the ventricular myocardium was complete. Similar changes recently have been described as occurring after transfusion of large amounts of citrated blood, and they were reversible with small amounts of calcium chloride.[10] The cause of the increase in the voltage and in the width of the T waves is not apparent. The change in the S-T segment is characteristic of hypocalcemia and probably is due to the citrate binding of ionized calcium. The changes in T waves in these experiments are difficult to evaluate because anoxia may be a factor, since the aorta was clamped and the heart continued to beat. Ventricular fibrillation followed a brief period of electrical alternans in dogs 1 and 2. In neither dog could fibrillation be stopped with second or third injections of sodium citrate, and release of the clamp from the aorta did not influence the rhythm. Cardiac

arrest was induced by an injection of potassium citrate, and the normal beat returned after release of the clamp from the aorta. In dog 3, 5 mEq. of sodium citrate slowed the heart rate from 90 to 40 beats per minute and P waves were not regularly seen. One gram of calcium gluconate injected into the machine increased the heart rate and restored the sinus rhythm.

It seems that the citrate ion in the amounts used for elective cardiac arrest was unable to stop heart action and appeared to promote ventricular fibrillation. We can find no support for Melrose's opinion[11] that the citrate serves a useful purpose.

Sodium lactate. To investigate the possibility that the sodium ion might have influenced the effect of sodium citrate, 5 mEq. of sodium lactate was injected into the root of the occluded aorta of dog 1. The T waves became larger and peaked and the Q-T interval increased because of increased duration of the S-T segment, but there was no fibrillation and no arrest (Fig. 2, *9*). The change in the T waves resembles that seen in mild hypokalemia. In dog 3 the injection of 10 mEq. of sodium lactate slowed the heart rate. In both experiments the injection of potassium chloride promptly stopped the heart action.

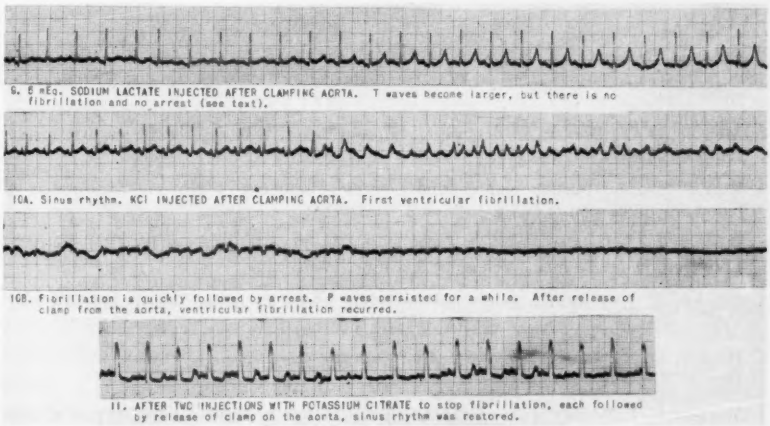

Fig. 2.

Potassium chloride. If, as seemed likely, potassium is the effective ion that arrests cardiac action, then equivalent doses either of potassium chloride or of potassium citrate should be equally effective. Potassium chloride was injected four times and each time it stopped the heart. In the first dog the ventricular arrest was preceded by a brief period of ventricular fibrillation (Fig. 2, *10A*), a sequence also commonly seen when potassium citrate is used. Ventricular fibrillation recurred after release of the clamp, but following rearrest normal rhythm was restored.

Summary

Experiments were done in dogs to demonstrate the effects of potassium and citrate ions on the heart under conditions similar to those existing clinically during elective cardiac arrest by the Melrose method. Potassium chloride seemed to be as effective as potassium citrate in producing cardiac arrest; thus, as expected, the potassium ion is responsible for this effect.

Citrate without potassium sometimes produced ventricular fibrillation which probably is a result of the binding of calcium. Since recovery from potassium citrate arrest is usually uneventful, a large series of experiments would be required to prove whether potassium chloride has less tendency to induce ventricular fibrillation than has potassium citrate.

An unusual type of 2:1 atrioventricular block was found when sodium citrate so prolonged Q-T intervals that alternate P waves occurred before repolarization of the ventricular myocardium was completed.

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